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The Journal of Laboratory and Clinical Medicine

VOL. III. ST. LOUIS, JULY, 1918 No. 10

ORIGINAL ARTICLES

TOLERANCE AND IMMUNITY

BY JOHN L. MARCHAND, M.D., PRINSAPOLKA, NICARAGUA, C. A.

VAUGHAN demonstrated some fifteen years since that the *protein poison* was a fact to be reckoned with in immunology; that the effects of this poison on the experimental animal could, under certain conditions, be other than deleteriously toxic. The rather voluminous literature of particularly the last two or three years on, especially, the treatment of typhoid fever, the arthritides and certain skin affections with nonspecific proteins, and with protein precipitating substances, administered in such manner, and in such dosage, as to elicit the maximum toxic reaction compatible with the welfare of the patient, offers undisputable evidence of the correctness of Vaughan's advancements. This authority, however, is either utterly ignored, or, for the most, misquoted when his work is mentioned at all.

Thus Miller,[1] one of the very few who mentions Vaughan's work, which he does in connection with his treatment of the arthritides with typhoid, and other proteins, given intravenously, misquotes him flagrantly when he states that the latter "observed that it was possible to produce in animals a transitory immunity to the colon bacillus by using peptone and egg-albumin, and that this immunity was apparently equal to that following immunization by the colon bacilli."

Now, while it is quite true that Vaughan did make use of peptone, egg-albumin and colon bacilli, these different proteins were employed in this instance merely for the purpose of extracting their *cell poisons* and for obtaining their *cell residues. It was with these poisons and residues, and not with the proteins themselves, that the series of experiments, undoubtedly referred to by Miller, were conducted.*[2] It is also true that, a few years previously, attempts had been made to produce an immunity with the cellular substance of the colon

bacillus; but this preparation proved so toxic, and the results of its administration so evanescent, that it was concluded that the capability of the animal to bear increased doses "was not sufficiently marked to be designated by the term immunity, and it was decided to recognize it as an increased tolerance."[3] No comparative studies with the other proteins named above, however, were made at this time; but it is of great interest to note that it was the then unrecognized phenomena of sensitization which principally interfered with the drawing of definite conclusions from this earlier work.

As a result of this later work, however, very definite conclusions were drawn. It was found that the cell poisons sensitized neither to themselves nor to the proteins from which they were derived, but that they did produce a certain tolerance, when introduced parenterally into the experimental animal, in properly gaged and properly spaced doses, which enabled these animals to withstand from two to three times the dose invariably fatal to the untreated animal; and, furthermore, it was clearly demonstrated in this series of experiments that animals thus treated with either the cell poison of the colon bacillus, with that from peptone or with that from egg-albumin acquired, in addition to this tolerance, a certain degree of immunity to inoculation with the living germ which enabled them to survive from two to four times the ordinarily fatal dose of the virus.

Quite in contrast with the cell poisons the cell residues proved to be ideal sensitizers, but to produce no tolerance. Animals sensitized with the cell residue of the colon bacillus acquired an immunity to inoculation with that virus which enabled them to withstand *at least eight times* the dose invariably fatal to the untreated animal; *but animals sensitized with the residues of peptone or egg-albumin showed no immunity to such inoculations.*

Tolerance, therefore, is designated as a nonspecific phenomenon, in that the tolerance produced by one protein poison is a tolerance to other protein poisons as well; and the transitory immunity accompanying, or conferred by, tolerance is equally nonspecific.

Sensitization, on the contrary, is regarded as a specific phenomenon, in that the sensitization produced by the sensitizing portion of one protein is a sensitization to that protein alone; and the immunity due to sensitization, *in every way superior to that due to tolerance,* is also specific.

In this series of experiments two very significant facts are to be noted:

1. In the poison immune animal, that is, in the animal treated with the poisonous portion of proteins, where a subsequent dose of a living germ which certainly would have proved fatal for the normal animal had been given, the symptoms were absolutely identical with those following a nonfatal inoculating dose given to the untreated animal. In other words, to quote Vaughan, "The similarity of the symptoms in the two instances leads us to believe that in all probability we are here dealing with an immunity which is identical in character with that which is usually spoken of as natural immunity." And natural immunity, which by no means could be called specific, is due to a mechanism which is at least intimately connected with the phenomenon of the phagocytic action of the white blood cells.

The tendency today to connect the results of nonspecific protein medication with white cell changes is very evident in recent publications.

2. When we come to consider the behavior of the residue immune animal after inoculation with its homologous living germ the reaction picture indicates an altogether different mechanism. In marked contrast with the normal animal after inoculation, where no toxic symptoms occur under an average of eight hours, the inoculated residue immune animal shows marked symptoms within an hour. After six or eight hours, however, the inoculated treated animal appears in good condition, in comparison with inoculated untreated controls, and eventually recovers, while the latter invariably die of the infection.

In other words, the normal animal and the poison immune animal react identically after the injection of the inoculating dose of virus, and not until after several hours, the former dying of the infection and the latter recovering; while the residue immune, the sensitized, animal, when specifically inoculated, reacts to the inoculating injection in a manner which strongly suggests by its character the reaction following an injection of the protein poison—that is, reacts violently, within an hour, but recovers and is not infected.

Surely these two immunities are not due to the same mechanism!

The most tenable reason for considering the reaction in the sensitized animal to be due to a specific proteolytic mechanism, and the symptoms of intoxication to be due to the liberation of the cell poison of the bacterial protein, is to be found in the fact that, while a reinjection of the cell residue is followed by absolutely no toxic manifestations, the cell residue containing no poison, a reinjection of an equal amount of killed homologous bacterial substance, which contains the poison in combination with the other cellular constituents of the bacterial protein, is followed by symptoms identical with those following an injection of the protein poison.

These unrefuted facts seem to entirely escape the notice of those who criticise Vaughan's theory; while they are met with silence at the hands of most others.

Clinically, the theory of protein sensitization, the development, *not in the blood*, but in the fixed cells of the body, during the course of an infection, or during the course of protein treatment, of a specific ferment capable of the cleavage of the infecting protein, or of one homologous to it, is upheld by many phenomena; among these may be mentioned that of the focal reaction, say, from the injection of tuberculin in the tubercular subject. Experimentally it is upheld, among other phenomena, by that of the response of the plain muscle of the virgin uterus of the sensitized guinea pig, freed from all traces of serum, when touched with a dilute solution of the sensitizing protein, as first demonstrated by Dale.

There is nothing incompatible with this theory, however, in the conception of a cleavage of foreign proteins by the normally present ferments of either the blood or the fixed cells. Indeed, the theory rests upon the ability of the normal ferments to do this very thing; and the specific cleavage action is considered rather an enhanced ability to digest a certain protein than an altogether new function acquired by the body cell—if my interpretation is not a fault. Neither is there anything in the theory which would not include a cleavage of foreign protein by the normally present enzymes of sufficient rapidity, given a sufficient amount of protein, to liberate a toxic dose of its cell poison. This, however,

would be dependent to a great extent upon both the physical state of the protein and the medium of its digestion—its mode of administration.

Thus, the cellular substance of the strain of colon bacillus used in Vaughan's experiments killed when coarsely ground in 1 to 50,000, and when finely ground in 1 to 75,000, or even as high as in 1 to 2,000,000, of the body weight of the untreated experimental animal; while the comparative toxicity of the same toxic protein when given subcutaneously and intravenously, and this includes the crude protein poison, is roughly 1 and 15—that is, such substances are from 10 to 20 times more toxic when given intravenously than when given subcutaneously. Although, as far as eliciting noticeable toxic effects intravenously, rather than fatal effects, is concerned, this may be done with possibly a hundredth part of the dose that causes toxic manifestations subcutaneously.

In nonspecific protein medication, then, we have a characteristic train of symptoms undoubtedly closely connected with the good results obtained, here following in the great majority of instances the most toxic mode of administration of toxic proteins, or of substances capable of precipitating the body proteins; and this train of symptoms is identical with the reaction after a mildly toxic dose of the protein poison given to the experimental animal, as near as it can be duplicated. This identity extends even to the necessity of increasing doses of the protein to produce subsequent reactions, if a subsequent injection is not delayed longer than a few days, or until the tolerance conferred by the poison liberated from the protein of the previous injection has waned. The blood picture is the same; the leukopenia accompanying the rise in temperature, and the leucocytosis, characterized by a relative polymorphonuclear increase, accompanying its fall.

And finally, accompanying, and probably due to, this blood change we have the amelioration of symptoms to a greater or less degree, corresponding to the "temporary immunity," mentioned by Miller, conferred on the experimental animal by treatment with the protein poison. Thus, all evidence seems to indicate that the benefits resulting from the, for the most, intravenous injection of nonspecific proteins are due to the effects of the cell poison liberated by the cleavage of these proteins parenterally, the protein poison of Vaughan.

Although not coming strictly under the head of nonspecific protein medication the work of Gay,[4] who ignores Vaughan's work, is of particular interest here. He treats typhoid fever with intravenous injections of a sensitized polyvalent typhoid vaccine sediment; and, although he apparently assumes his sediment to be nontoxic, in that the "endotoxic substances" are extracted, its exhibition is followed by a reaction in no way differing from those following injections of "unextracted" proteins. In the preparation of this vaccine the multiple strain typhoid bacilli are killed and precipitated with alcohol, and then ground to disintegration; the "endotoxic substances" are then extracted by means of carbolated saline, *and the supernatant fluid rejected.* The sediment remaining only is used.

As a method of detoxication, if this is really the object of the above procedure, a comparison of the effects of the "sediment" of Gay, as evidenced on the typhoid subject, with those of the "cell residue" of Vaughan, obtained by extraction with alkaline alcohol, as evidenced on the guinea pig, will show the

latter to be a far superior method of detoxication, and that, at least in comparison with the cell residue, the sediment is a highly toxic substance.

The cell residue of the typhoid bacillus is absolutely nontoxic for either the unsensitized or sensitized guinea pig in doses of 100 mg. or more when given intraperitoneally—corresponding to about 50 mg. intravenously—and it is very active as a sensitizer. The sediment is toxic for the typhoid patient in doses of 0.02 mg. intravenously; so that, it is very active as a toxic agent at least, and apparently so as a sensitizer.

According to Vaughan, all proteins are toxic parenterally, and *the toxicity of a protein is dependent rather upon the rate of its cleavage than upon its amount;* so that, then, the dose of a vaccine would depend upon two things—the physical state of the protein it contains, and the capability of the recipient for its cleavage parenterally. The fact must not be overlooked, however, that this cleavage may be so rapid and so thorough as to digest the poison itself, converting it into nontoxic bodies. This undoubtedly explains why a sensitized vaccine is less toxic for its specifically sensitized animal than it is for the normal animal[5]—the vaccine, being sensitized, is digested with greater ease, and the animal, being sensitized, digests the homologous protein more rapidly.

Despite his clear demonstration of the beneficial influence of the cell poison upon the resistance to infection in the experimental animal, Vaughan has condemned toxic vaccines. This I consider his one inconsistency. The ultimate test of any theory of immunity, however, must rest with its application clinically. Animal experimentation at best can furnish but a more or less general idea of the effects parenterally of foreign substances upon the human organism, and more especially upon the infected human organism; and this applies with even greater force to the so-called immunity reactions *in vitro,* which take into consideration the defensive mechanism of the blood alone.

Now, if the conception that the parenteral introduction of protein matter may be followed by the activation of the protein poison is correct, then the effects of this poison upon the infected human organism, in contrast with its effect upon the infected experimental animal, are not always deleterious; in fact they are often decidedly beneficial.

The truth of the matter seems to be that the degree of tolerance which different organisms are capable of producing varies, other things being equal, directly with the mass of the organism. The infected laboratory animal has evidently produced tolerance, as a result of the cleavage of the infecting protein, to the full extent of which it is capable; so that, any additional poison, no matter how minute in quantity, or whether given in the form of the cell poison, or in the combined state, as in an homologous protein injection, only hastens the infectious process.

As undoubtedly shown by Gay, the results of the specific treatment of typhoid fever are relatively better than those obtained from its nonspecific treatment. No tenable reason is given for this, however; for the following statements, very evidently made in support of his preference for a specific protein medication, seem to be casual rather than to hold any intended causal significance. These three statements are as follows: (1) The typhoid vaccine *"in addition"* to the benefit derived from its nonspecific reaction *"aids in establishing an active"*

(prophylactic) *"immunity against the microorganism concerned."* (2) *"Relapses were distinctly reduced in those cases in which the intravenous injections were followed by a series of three subcutaneous inoculations after the temperature had reached normal."* And of prime significance, if a difference in the average reaction picture from that produced in the normal subject is meant, (3) *"these vaccine injections"* of the regular prophylactic dose, 0.1 mg. subcutaneously *"in the convalescent typhoid will in a few instances cause a rise in temperature of a degree on the same or following day."*[6]

Yet, either of these three statements realize a tenable explanation as to why the specific treatment of typhoid is superior to the nonspecific. This may be summed up in one word *sensitization;* and, in this particular instance, the superior sensitizing qualities of a polyvalent, sensitized, disintegrated typhoid protein over a monovalent, untreated, unground preparation.

With nonautogenous preparations at least, the polyvalency of the vaccine would undoubtedly relatively increase its specificity to the infecting bacterium, and, therefore, enhance its *specific* sensitizing qualities as well as its toxicity; the sensitization of the vaccine would probably increase its sensitizing qualities and, as Gay states, its toxicity as well; the distintegration of the bacterial protein would undoubtedly increase both its sensitizing and its toxic qualities, while, by the rejection of the supernatant carbolized saline solution used in its extraction, both the sensitizing and toxic qualities of the vaccine would undoubtedly be reduced, and reduced, moreover, in direct relation to the fineness of the ground protein, either in suspension or in solution, carried off with the extracting solution. But that there is any appreciable *free* poison either extracted or carried off in this process, from the light of, particularly, Vaughan's work in the extraction of proteins, is extremely improbable.

I have thus, perhaps not too theoretically, discussed the Gay-Claypole Vaccine Sediment for the reason that, although I have had no experience with this preparation, I have been working for a number of years with vaccines which might correctly be called antithetical to this preparation, in two important respects at least. These preparations are unsensitized, and *they may be said to correspond exactly with the supernatant fluid discarded by Gay in the preparation of his vaccine*—all bacterial substance they contain is, at least, ultramicroscopical. On the other hand, these preparations are polyvalent, and unqualifiedly specific in that each one sensitizes, and sensitizes efficiently, only against itself, or against an homologous protein, and sensitizes more readily intravenously than subcutaneously.

From the fact that of these preparations each contains practically an equal amount of bacterial protein in the same state of suspension or solution it has been possible to ascertain that no two of them sensitize with the same facility—in the same space of time, or with the same number of treatments, even, apparently, when the same dose of each can be employed, which is not always the case—and that the duration of the state of sensitization against each protein preparation seems to vary inversely to the facility of its production. This duration is a matter of a few months with some of these proteins, and, undoubtedly, of years with at least one other.

These preparations are highly toxic, and being much more toxic intra-

venously than subcutaneously they produce, or enhance, tolerance more quickly when given intravenously; although this can be accomplished quite readily by the subcutaneous method. They produce local reactions when given subcutaneously, but these are diffuse in character and not severe, excepting those following large doses; for they seem invariably to correspond in severity with the constitutional effects from the injection. Given relatively the same degree of sensitization against either of these proteins, and the same dose of each, the character of the reactions, locally and systemically, is exactly the same—that is, one protein seems not a bit more, nor less, toxic than either of the others, produces the same degree of tolerance, and the tolerance following the reaction from one protein is a tolerance to the reaction from either of the others, is of no longer duration, nor differs in any other respect. In contrast with sensitization, this tolerance, by whatever protein produced, if following a single injection has very perceptibly waned by the fourth day; after a series of injections, however, it is of longer duration, but never seems to last longer than two weeks at the most.

Some hundred cases of tuberculosis, among which a few were apparently so acute, many so far advanced and some apparently so hopeless, as to materially affect favorably their amenability to a then not always pleasant mode of treatment, to an extremely rigid regimen and to a monotonous routine of keeping thrice-daily temperature and pulse records, along with other data, furnished the material, in forty-two cases, from the careful study of which the conclusions were definitely settled that *toxic vaccines*, contrary to Vaughan's statements otherwise, are not only the vaccines of choice, but are often actually the vaccines of necessity for the successful treatment of the infections; and that the correctness of his contention that active immunity against a given bacterium, and sensitization against its specific protein, are identical, can be tenably supported clinically.

Every single one of these forty-two cases of tuberculosis gave a more or less frank initial focal reaction to the tuberculoprotein in varying but infinitesimal amount; all of them, with the exception of three, reacted systemically, and about half of them focally, to one or more other bacterial proteins, administered mostly subcutaneously, in varying but much larger doses than were necessary with the tuberculoprotein to elicit the same class of reactions, and two of them reacted systemically to the protein of horse serum.

The tubercle bacillus was found in the sputum, or in other specimens, from the majority of these cases, but not in all; the uncomplicated, early, but well defined, apical and the closed joint cases furnishing most, if not all, of the exceptions. And, although the bacterial flora of well selected sputum or other specimens did act as a certain guide in determining the secondary infectors, the great majority of bacteria here found, and particularly with the sputum, proved apparently to be saprophytic.

On the other hand, neither was the fact that a subject reacted systemically, or locally, to a certain bacterial protein taken as conclusive evidence that the homologous bacterium was present as a secondary infector, even when this bacterium was found in a specimen examined. Only the frank focal reaction from a single injection of such a small amount of bactertial protein as to cause

no, or very mild and evanescent, systemic symptoms, and the secondary focal reaction, of tardy onset, following a single injection, or a series of injections, where the reaction systemically was also absent, or very mild but *protracted,* were regarded as specific, and, hence, as evidence that the homologous bacterium was present as a part of a multiple infection.

The so-called secondary focal reaction, that tardily following, as a general thing, the more or less protracted administration of proteins, bacterial or otherwise, and associated with a high and protracted toxicity, can not be regarded as specific, or at least as strictly so. It may be caused by any protein to which the patient will react regardless as to whether it is homologous to the infecting bacterium, or to one of the infecting bacteria of a mixed process, or not. There is no excuse for the administration of vaccines in doses causing such reactions, and the focal manifestations following such systemic reactions should be regarded rather as an exacerbation of the process, than as a reaction. This phenomenon has for its analogy, without doubt, the deleterious effects produced in the infected experimental animal after injections of the protein poison, as demonstrated by Vaughan, and is a nonspecific accident.

As the specific focal reaction, the secondary being practically a protracted form of the primary, will enter largely into the discussion to follow, some consideration as to its probable mechanism, as well as to its significance based thereon, would doubtless be desirable.

Just what determines the predilection of certain proteins for certain organs or tissues is not known; but it is a well recognized fact that not only living pathogenic bacteria infect, show a preference for living, growing and multiplying in, certain tissues, but that these same tissues act as predilection points where these same bacteria deprived of life will be deposited, if injected into the blood stream, and where they are slowly digested. In this manner the cells of these tissues are educated to digest this particular protein, and are then said to be sensitized.

It is easy to conceive of an infected area, in which bacteria are not only living and multiplying, but also dying, becoming highly sensitized in comparison with other, and especially the more distant tissues in less intimate relation with the sensitizing protein; and, if not too completely walled off from the general circulation, of homologous protein introduced parenterally being carried by the blood stream to this sensitized predilection area to be there broken up with the symptoms usual with such cleavage, those of inflammation, in such tissues. These *protein cleavage symptoms* constitute the primary focal reaction; but they are not the only effects from proteins focally. Those from the *protein cleavage products,* or from one of them at least, must receive an equal, if not a greater, consideration.

Any attempts to determine the effects of proteins upon the experimental animal by the parenteral introduction of unbroken proteins can only be considered, since the epoch-making studies of Vaughan, on a par with suppositional efforts to arrive at the definite effects of, say, morphine and apomorphine, by the direct employment of the crude opium from which both are derived. The former procedure is just as irrational as would be the latter, yet it is still being resorted to almost exclusively in immunity studies, both experimentally and

clinically. A doubly flagrant example of this has already been cited in Miller's misquotation of Vaughan's clearly expressed exposition of his well defined work.

In the light of the generally conceded correctness of the observation that an excess of sensitizing protein delays the onset of the sensitized state; of that of the specificity of the refractory condition so clearly demonstrated in the animal sensitized simultaneously to two different proteins, but more especially of the two following demonstrations by Vaughan, it is very evident that the effects of the nontoxic cell residue, the sensitizing portion, of bacterial proteins used as a specific therapeutic agent may not always prove beneficial to the infected subject.

These demonstrations are as follows: 1. It was found that, when injected abdominally into fresh guinea pigs, 25 mg. of colon residue, and 12.5 mg. of typhoid residue, in the short space of thirty minutes, had conferred immunities, in the former case of five, and in the latter of six units; *but that larger doses did not give such good results.* This was tenably explained by supposing that the ferments activated by the residues, for, according to this theory, the ferment is stored in the cell in an inactive state, were in part used up in their reactions with the residues themselves—a relative exhaustion of specific enzyme in each instance, which allows the growth of the inoculated virus.

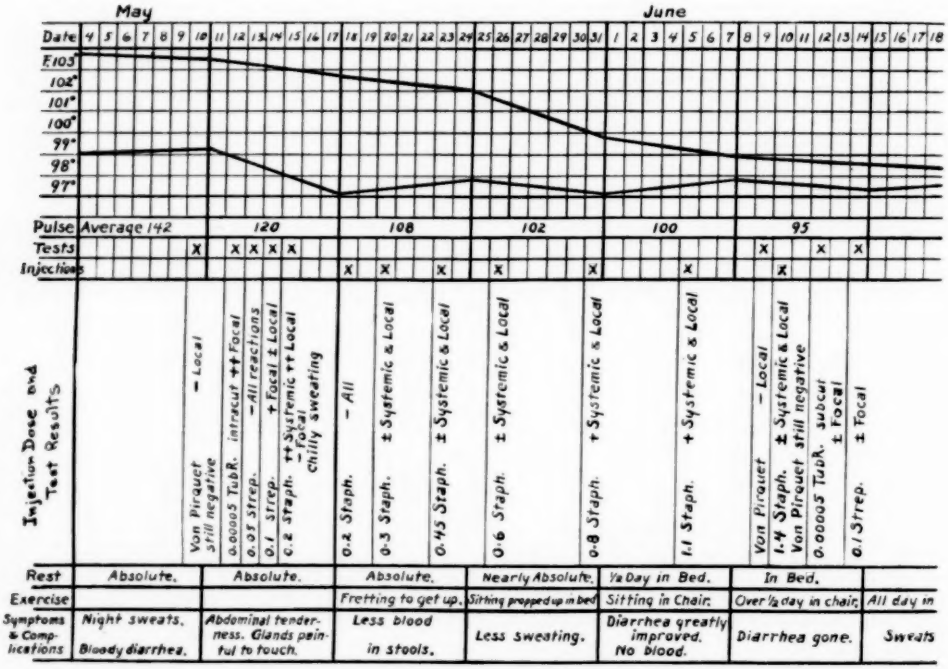
2. It had been found during two years of treating tuberculosis with the *nontoxic* cell residue of the tubercle bacillus that, if properly used in initial cases, its action was prompt and apparently specifically beneficial; but that in advanced cases it was of no benefit. Of more importance here, however, is the fact that, even in initial cases, *it would prove harmful if given in too large doses, or in small doses too frequently repeated.* The same tenable explanation, it would seem, is equally applicable here.

The tubercular subject possessing systemic sensitization, extrafocal ferment, incapable of the complete cleavage of a large dose, or of smaller too-often-repeated doses, of the tuberculoprotein, here the specific portion of this protein, this specifically active portion is carried to the more highly sensitized predilection point, the focus of the infection, where it uses up the focal ferment in its reaction with this body, with a consequent activity of bacterial life, a more active process, to the detriment of the patient.

This also explains the secondary focal reaction, which is really an exacerbation of the process of a specific causation; and it is to be noted that its determination from the pseudosecondary focal reaction, previously cited, which is of nonspecific causation, the poison, is often made with difficulty when toxic proteins are being employed. This distinction can be fairly well made, however, by noting the character of the systemic reactions immediately following the injections: if these are sharp and evanescent, both the vaccine and its dosage may be said to be beneficial; if they are sluggish and protracted, the secondary focal is indicated, and if they are sharp and protracted, there is the question of an overcome tolerance to be considered—never overlooking the fact that a retrograde of the patient's condition may be due to a double focal cause, both the specific and the nonspecific. Fortunate, indeed, is the tubercular case who gives frank focal responses to proteins used therapeutically; and, by the same token,

who gives equally frank focal manifestations as a result of overactivity and other indiscretions.

If these interpretations of the focal phenomena are correct, and in support of this I refer the reader to Vaughan's "Protein Split Products," recommending a careful study of his own work, and of his interpretation of most of the work of others done up to the time of its compilation, then, the focal reaction, if it can be elicited frankly and evanescently, offers a sure and safe means of gauging the degree of *extrafocal* sensitization present in the infected subject. And, bacterial immunity produced in an infected organism is, without doubt, dependent upon the degree of systemic sensitization attained by the organism against the homologous protein of the infecting bacteria; and the degree of sensitization, as long since pointed out by Vaughan, can not be measured in the test tube.

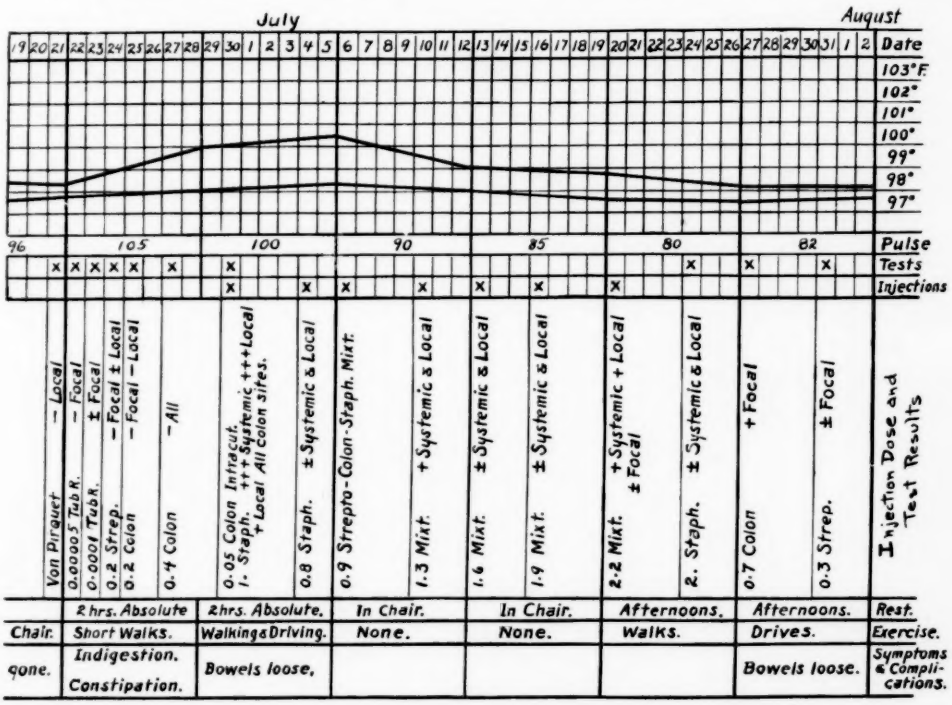


The case to be cited, in further support of this view, and of other views, especially regarding toxicity, one of some twenty in whom immunities were established in from nine months to two years, differs from most of the others in but one or two respects—the absolute frankness shown by almost all reactions to vaccines, and his perfect willingness to subject himself to all manner of tests, some forty of which were applied. These cases were all of a certain sameness verging on the monotonous; if tolerance could be enhanced, either by vaccines or by a combination of vaccines and regimen, they all improved; if not, they died more or less promptly. And, here let it be said, the number in whom it proved impossible to establish an efficient tolerance by a combination of the above procedures was as 1 to 4 or 5 of those who wouldn't, or didn't, for one reason or another, "play the game" after improvement had become more or less marked.

This case was that of a man of 27, married, by occupation a mule driver in a coal mine and with a history of exposure to tuberculosis through a sister who had died some time previously of an acute pulmonary process. Another sister, later on, also developed pulmonary tuberculosis; and his wife, still later, strongly evidenced an initial pulmonary infection.

A month or two previous to coming under my care the patient had undergone an ill-advised operation for appendicitis, and subsequently had developed not only an apparently acute pulmonary process, but a multiple submaxillary and cervical adenitis, as well as a diffuse peritonitis. He had been sent home from the hospital to die.

Several of the involved glands had been evacuated while he was in hospital,



and at the time of my first examination it seemed that several more were approaching the stage of dissolution. This, however, did not occur.

He had the appearance, and evidenced the symptoms, both subjective and objective, of an advanced and complicated case of the fulminant pulmonary type, with well defined cavity formation in one lung as the most striking sign of this.

His abdomen was tender and swollen, and he had, and had had for several weeks, an intractible bloody diarrhea. No examination was made of his excreta.

His cough was almost constant, but efficient in that it raised an abundance of purulent, greenish colored, foul-smelling sputum which was tubercle positive, and contained in addition myriads of other bacteria, the streptococcus, staphylococcus and colon bacillus predominating.

His blood pressure was low, his temperature high and his pulse rate rapid

and irregular. Night sweats were constant, and, next to his cough, were the most distressing of his symptoms.

Very little was gained, apparently, from a more rigid regimen; but from a change into more cheerful surroundings and into a larger, more airy, better lighted room, he was certainly better contented.

A week was spent in impressing the patient with the absolute necessity of a strict and protracted adherence to his regimen, in getting him intelligently interested in his case, and in accustoming his mother-nurse to the keeping of an absolutely accurate record. He was then tested for his focal tolerance, his systemic sensitization against, three bacterial proteins—the tuberculoprotein, the streptoprotein and the staphyloprotein. The results of these tests, shown on the case chart, were as follows:

May 10.—A von Pirquet was negative, and so remained.

May 12.—0.00005 c.c. tuberculoprotein, given intracutaneously, produced a well marked focal reaction in both lungs—pain, increased sputum with a little blood—and an increased tenderness over the abdomen. There were no appreciable manifestations of any other kind, and these symptoms subsided during the late afternoon.

May 13.—0.05 c.c. streptoprotein, given subcutaneously, caused no, at least immediately, noticeable response.

May 14.—0.1 c.c. of the same protein caused a very slight redness locally, no marked pulse or temperature variations, but a decided focal response in the lungs, as well as an increased tenderness over the enlarged cervical glands.

May 15.—0.2 c.c. staphyloprotein caused a rise in temperature of 2 degrees, a pulse rate increase of 14, a decided feeling of chilliness followed by sweating and a marked local reaction. No focal manifestations of any kind were noticeable.

This mild but characteristic reaction picture, here following the subcutaneous injection of the protein, was followed the next day by a feeling of decided well-being that continued until the third day, when the temperature began to rise again. From this on injections of the staphyloprotein were given subcutaneously in doses increased each time from 0.1 to 0.3 c.c., and at intervals of from three to five days, until June 10, when 1.4 c.c. was given. This last injection caused a slight rise in temperature and a mild local reaction.

But this reaction picture was not the only thing characteristic of this treatment; besides the well marked amelioration of all untoward symptoms, the variations in temperature and the blood pictures were equally characteristic with the classic reaction picture of this class of tubercular patients *when improving under this treatment.* These will now be considered in their probable order of importance as readily available clinical guides, or controls for the management of vaccine treated cases.

During the week previous to the tests with the bacterial proteins the mean high, or evening, temperature was 103.7°; and the mean low, or morning temperature 99°—representing a mean difference of 4.7°—and this had practically obtained during a few previous weeks.

During the week these tests were being applied the mean high temperature was 102.7°, and the low 97.3°. A mean difference of 5.4°; a fall in high temperature of 1, and in low of 1.7°.

The week following the last injection of this series, the 1.4 c.c. staphylo-

protein given June 10, shows a mean high temperature of 98.7, and a mean low of 97.7°. A mean difference of 1°; a fall in mean high temperature, which was steady, of 4°, and a rise in mean low temperature, which fluctuated, of 0.4°.

In comparison, it is interesting to note that, four months later, during his treatment with injections of the tuberculoprotein, and after having had practically no reactions of any kind soever for a period of three weeks, his mean temperatures were, high 98.2°, and low 97.66°—a difference of 0.54°. This may be considered as about the normal variation for this case, without doubt. Subsequently, however, when it became necessary to resume other proteins in his further treatment, and systemic reactions were produced, by any protein, including the tuberculoprotein, this variation again increased; but, no matter how severe the reactions, or for what length of time the series of injections lasted, this difference between mean low and high temperatures never exceeded 1.5°, and quickly lessened with each discontinuance of reacting doses of proteins. This is in marked contrast with the initial difference of 4.7°.

That the process of testing the patient to the three bacterial proteins, as described above, had a salutary effect, there can be little doubt; and that this effect was not due wholly, or even to a great extent, to the injection of staphyloprotein on May 15, but in part to the other proteins used previously, is equally obvious. The fall in temperature after this test injection of staphyloprotein was not sufficiently marked to account for the reduced mean temperature occurring during this week; in fact, its tendency was to raise this average.

It must be remembered that the two proteins used in the previous tests were "specific" to his mixed infection; that is, that they caused focal reactions, frankly so. In spite of this, the tuberculoprotein of both the Pirquet and the intracutaneous injection seemed to "flatten out" the high temperature line, and to steadily reduce the low temperature from supernormal to normal, or even subnormal. The behavior of the streptoprotein was somewhat different; for, just as it caused both focal and systemic phenomena, for the local reaction was a mild sign that the latter was really the case, its effects upon temperature seemed to simulate that of the tuberculoprotein upon the low, and that of the staphyloprotein upon the high temperature.

These phenomena could be summed up probably best in the following tenable conclusions. A "certain state of focal activity," whether produced by vaccines capable of producing focal reactions, or by a certain amount of activity on the part of the patient, here including even the change from the horizontal position to the semiprone of sitting propped up in bed, or by a combination of the two, was invariably followed by a flattening of the high temperature line, and by a gradual decline in the low temperature line, which latter quickly tended to reach normal, or subnormal. These manifestations, however, were not of sufficient intensity, or so striking, as to be called reactions. These phenomena must certainly be regarded as beneficial, and of a specific mechanism; although they are incapable of anything but transitory benefit unless produced under the protection of an efficient tolerance.

The phenomena following the administration of the protein not specific to the process, at least in that it caused no focal manifestations, the staphyloprotein, were in marked contrast. Here, these were manifested only after such doses as would cause systemic reactions; and they were characterized, after the re-

action rise, by an immediate and continued effect on the high temperature line, which gradually declined. The effect of these systemic reaction-causing injections on the low temperature line was exactly the opposite. The transitory reaction rise of the high temperature line had its corresponding transitory fall of low temperature the next morning, rarely for two succeeding mornings; but the general, though less regular and steady, trend of this line was from the subnormal to the normal. And, if my interpretations of the observation of many carefully controlled cases are correct, the less regular and less steady trend of this low line from the subnormal to the normal is due to that "certain state of focal activity," which is mentioned above as the probable cause of the gradual decline of this line from the supernormal to the normal, here probably a greater activity.

Among the probable causes of such focal activity, fretting and tossing in bed, both of which this patient did, are of equal importance with those already mentioned. Needless to say, however, these finer temperature variations are only to be noted with any degree of accuracy with the patient at absolute rest, thoroughly under control and carefully watched; and an absolutely essential aid in drawing conclusions is a carefully and properly kept record.

To recapitulate, a certain amount of focal activity, then, undoubtedly makes for a fall in the mean low temperature line from the supernormal to the normal or subnormal, in the early treatment of the advanced tubercular; and this can be considered only as beneficial. A further focal activity, no matter what its cause, tends to keep this line subnormal. A still greater focal activity, probably for the reason that secondary focal phenomena are then manifesting their influence, makes for a rise of this line to again the supernormal mark, just as these so influence the high temperature line also. I shall cite an example of this in connection with testing this case with the colon protein. Needless to say, this rise of average low temperature to the supernormal can be regarded only as deleterious.

I have no explanation to offer as to the exact mechanism of these repeatedly noted phenomena, other than that they are of a specific character, and of focal origin; but as to their significance there can be no doubt. They are considered of sufficient importance to be employed as a certain control in the management of at least the early treated advanced tubercular subject.

During the fourth and last week of this series of staphyloprotein injections the patient was given three tests; a Pirquet was applied the day before the last injection was given, and a subcutaneous injection of 0.00005 c.c. tuberculoprotein was given on June 12, and 0.1 c.c. streptoprotein on June 14. These were the same doses of the same proteins given exactly one month previously; and, as with these previous tests, the Pirquet was negative and both injections caused focal manifestations, although probably less severe than on the former occasion.

The patient was now given a week of rest from active treatment, and during this time he was gradually accustoming himself to spending his days in a chair. By this time his night sweats had ceased; blood had disappeared from his stools, and these were now of normal consistency and regularity. In addition, his cough was no longer troublesome, his sputum had become much reduced in quantity and was now only streakedly yellow; it had lost its foul odor

and contained a very perceptibly reduced number of bacteria, especially of the streptococci. Moreover he had gained materially in weight and appearance.

At the end of this week of rest his temperature was again on the upgrade. A Pirquet was applied, again with negative results; but he now tolerated 0.0001 c.c. tuberculoprotein with but faint focal manifestations, and 0.2 c.c. streptoprotein without the slightest signs of any such phonemena. This latter protein, however, did cause a possible slight rise in temperature with a mild local reaction.

About two weeks, then, after the last of nine subcutaneous injections of staphyloprotein, extending over a period of four weeks, during which his sensitization against this protein increased about 120,000 units, the patient had gained in sensitization against the tuberculoprotein to the extent of about five units, and against the streptoprotein about 10,000 units. And here be it understood that the word "sensitization" is not strictly applicable in describing the increased "tolerance" of the patient to the staphyloprotein. This was undoubtedly due in great part to increased sensitization, but to some extent also to the tolerance of the poison he had acquired through his previous injections. That this tolerance existed at the time of the last injection of the series, 1.4 c.c., which caused a mild reaction, and that it had practically disappeared twenty days later, was evidenced by the overwhelming reaction following 1 c.c. of the same protein then given. The focal reaction, as evincing the degree of sensitization, would probably have been absent with any safe dose of this protein.

Why this gain in sensitization against the tuberculo- and streptoproteins was not evident immediately after the last injection of the series of staphyloprotein injections can not possibly be explained by the influence of tolerance, as can be readily seen; but it might be explained here, and in similar cases, and very tenably so, by supposing that the body cells no longer being subjected to the influence of the more readily sensitizing staphyloprotein of the injections were now being stimulated by the less readily sensitizing autovaccines of the tuberculo- and streptoproteins of the infecting bacteria to the end that a further sensitization against these bacteria was now being produced. This would presume that the autostaphyloprotein had been cleared up by its specific treatment; and, indeed, evidence of this existed in the almost total absence of staphylococci from the sputum, if not in the general improvement of the patient. Evidence of this increase in sensitization, however, can at times be elicited immediately after such a course of vaccines.

In testing with the colon protein, at the expiration of his rest period, it was found that neither 0.2 c.c. nor apparently 0.4 c.c. of this protein caused the slightest reaction of any kind; so that, some doubt existed as to whether the colon bacillus was responsible in part for the mixed process, or, as would naturally follow, whether he was sensitized to this protein.

The high temperature line alone seemed to be affected by these two injections; but, as the patient had been increasing his activities a little too rapidly, and was living more quietly at this time, it was a matter of doubt as to whether the gradual fall in temperature which then occurred, a matter of a degree, was not due to this rather than to the vaccine. To ascertain which was the real cause an intracutaneous injection of 0.05 c.c. colon protein was given on June 30, and

this was followed immediately by a subcutaneous injection of 1 c.c. staphyloprotein.

The severity of the reaction caused by this injection has already been noted. The temperature rose 5°, and there was a decided chill followed by sweating, as well as a very severe local reaction. The site of the intracutaneous colon protein injection, on an entirely different part of the body, and not near the sites of the previous subcutaneous injections of this protein, lighted up and showed distinctly positive, as did the sites of the two subcutaneous injections also. This phenomenon will be discussed a little later.

Theoretically this dose of staphyloprotein was correct; practically it was too large by far; for no account was taken of the different conditions under which the patient was then living in comparison with the time when 1.4 c.c. of this protein had caused only a moderate reaction. He was decidedly more active, and partly as a result of this autointoxication had already overcome the tolerance then existing, for he was evidencing a gradually rising temperature. And, as it is the liberated poison above tolerance which causes the reaction, he practically got the full effects of a very toxic cleavage of the total dose; for his sensitization against this protein was then, without any doubt, high.

Very little significance was placed at the time in a decided looseness of the bowels which set in after this reaction. This was attributed, as was the four day rise in temperature, *both morning and evening*, although the latter to a much greater extent, naturally, to the severe reaction. This then seemed a correct conclusion as these untoward symptoms quickly subsided after another injection, now of 0.8 c.c. of staphyloprotein on July 4, which caused a mild systemic and local reaction. Later, however, undisputable evidence that this was a focal manifestation, *secondary in character*, possibly caused by the colon protein of the two injections, and probably aided and abetted by the severe reaction, was found, and in this manner.

He was now given a little over two weeks of treatment with a mixed vaccine composed of one part strepto-, two parts colon and four parts staphyloprotein, to all of which he had reacted. This series of five injections started with 0.9 c.c. and ended with 2.2 c.c. of this mixture. The last dose caused not only a mild systemic response, but focal manifestations as well—frankly, by a decided abdominal tenderness, questionably, by an uncomfortable feeling over the chest. The only other sign of this was a slight rise in mean morning temperature—but, as already stated, with even a moderately active patient not much dependence can be placed in these delicate variations when they occur alone. Here, however, this questionable additional evidence of focal activity was not needed; for some reason he now frankly evidenced focally a too large dose of one, or more, of the proteins of the mixture.

The question now was which of the three bacterial proteins had caused these focal reactions. To this end, and although two alone were suspected, a subcutaneous injection of 2 c.c. staphyloprotein was given four days later, July 24. This caused only a mild response locally. On July 27 0.7 c.c. colon protein elicited a frank focal response in the form of a slight abdominal tenderness and a slight tendency to diarrhea, no temperature variations were noticeable. On July 31 0.3 c.c. streptoprotein caused a mild tenderness of the cervical glands

and a decided feeling of oppression over the chest, but no temperature variations.

Undoubtedly two of the proteins, the colon and the strepto, were in part the cause of the focal manifestations following the mixed protein injections; while the temperature excursion, partly at least, and the diarrhea following the tests with the colon protein were undoubtedly due to a mild exacerbation, a secondary focal reaction, probably brought on by, if not directly due to, the two injections of the colon protein given a few days before, and from which no reactions of any kind were noticed.

Four weeks were now devoted to careful tests with the different proteins, the while the patient observed a strict regimen, especially as to exercise and rest. The results of some of these tests, those most pertinent to the question, with their discussion, follow.

A Pirquet was again applied, Aug. 21, and this remaining negative, a subcutaneous injection of 0.9 c.c. staphyloprotein was given two days later. This was followed by a reasonably severe systemic reaction with local manifestations, while the Pirquet lighted up and showed strongly positive.

It is a well recognized fact that, other things being equal, the tubercular subject who shows a frank local response to the tuberculoprotein, whether exhibited in the form of a Pirquet or an intracutaneous, or subcutaneous, injection being immaterial, as the mechanism is the same in each instance, is the subject who, as a general thing, responds the most readily to treatment. This is undoubtedly due to the fact that such a subject possesses a relatively high degree of sensitization against the tuberculoprotein. But that there are some other cases not so reacting to the tuberculoprotein who respond equally well to treatment is equally true; and this case was one among this number.

Despite the evidence that the local reaction is determined by the *cleavage* of proteins, and not by the *products* of their cleavage, it is very evident that tolerance, *produced by a protein cleavage product*, does have a certain effect upon the local reaction.

It had been noted times without number that a Pirquet, or the site of an intracutaneous, or of a subcutaneous, injection of tuberculoprotein, showing negative, would often light up and show positive after the injection of another, or of the same, protein given in such dose as to cause a systemic reaction; in other words, by overcoming the then existing tolerance. This nonspecific, and specific, lighting up of injection sites had been noted with other proteins as well, and was demonstrated previously in this case, nonspecifically, by the lighting up of the intracutaneous site of the colon protein injection with the systemic reaction following the subcutaneous injection of staphyloprotein, already cited, and it was really demonstrated specifically by every local reaction that occurred.

The fact that the sites of the subcutaneous injections of colon protein also lighted up with this supplemental injection of staphyloprotein, since one had been given four, and the other six, days previously, should have indicated what was the probable reason for the absence of reactions systemically, to the extent at least of preventing the further employment of this protein, and especially in a mixture. Had this occurred a little earlier in the treatment, the results might well have proved disastrous.

The negative Pirquets, and the negative intracutaneous injection of tuberculoprotein, in this case were interpreted, especially after their failure to light up with the reactions of supplemental injections, as showing that the patient possessed insufficient extrafocal, or systemic, sensitization against the tuberculoprotein to break this protein up with sufficient violence to cause local manifestations of inflammation—and proteins, the tuberculoprotein in particular, are broken up possibly the most slowly in the skin, just as they are probably broken up the most rapidly in the blood stream.

And the same interpretation, somewhat modified, should have been made in the case of the colon protein—a temporary exhaustion of its specific ferment, due possibly to digestive disturbances, which the patient really had at that time. So that, the colon protein, instead of being beneficial, as would be judged by the fact of its producing no reactions, while the temperature seemed to be affected favorably, was really doing harm. I have no explanation as to why this protein failed to produce focal manifestations frankly in this particular instance, and then did so later; and especially is this puzzling as the frank focal manifestations occurred after a mixed vaccine, and not with the straight. My experience has been to expect just the opposite, which is one reason that I consider mixed vaccines dangerous.

This, the fourth application of the Pirquet showed positive, but only after a supplementary injection which produced a systemic reaction. An unsupplemented local reaction from the tuberculoprotein was not noticed with this particular patient until the dose of this protein had reached 0.4 c.c.—and, it may be added, that he had then had no injections of other proteins for close on to seven weeks, and was living under a careful regimen; so that it required very little in the way of a dose of protein to overcome what tolerance then existed.

Special care was always exercised in giving the tuberculoprotein injections to have a certain amount deposited within the skin, as well as to avoid previous injection sites; so that, with the largest dose reached with this protein, and after a few repetitions of this dose had ceased to show a reaction of any kind, it was superfluous to apply a Pirquet, or to give an intracutaneous injection of this protein to furnish additional evidence that the protein both in the skin and under the skin was being digested so readily and so thoroughly as to cause no symptoms either from its cleavage or from its cleavage product.

It is of significance to note that, over one year after the patient had received his last tuberculoprotein injection, an intracutaneous injection of 0.05 c.c. of this protein, even with a supplemental injection of a strepto-mixed vaccine, to which he was still partially sensitized, and which caused a rather sharp systemic response, absolutely failed to light up. So that, the Pirquet, or its analogies, irrespective of the influence of tolerance, will show negative, then positive, and again negative, *as sensitization advances.*

That this was undoubtedly happening with this subject there is other and abundant evidence. Part of this evidence is shown by the results of the other tests made at the time of the positive Pirquet. On Aug. 25 he was found to tolerate 0.5 c.c. streptoprotein, and on Aug. 30 0.0008 c.c. tuberculoprotein was tolerated equally as well; while a little previous to the application of the posi-

tive Pirquet he was found to tolerate 0.7 c.c. colon protein, which then gave a systemic response.

I have already shown the increase in sensitization against the tuberculoprotein during the first series of injections, four weeks of treatment with the staphyloprotein, to have been about five units; while now, after seven weeks of regimen and testing, including the second series of injections, three weeks of staphylocolon-streptoprotein treatment, his gain in sensitization against the tuberculoprotein is more than 70 units.

This obvious increase in gain of sensitization during the second series of injections over that obtained during the first series, absolutely does not evince any superiority of the mixed vaccine over one of a single kind of bacterial protein, a *straight* vaccine, such as was the streptoprotein used during the first series of injections; but, in my opinion, which is based on controlled observations of many cases treated with both straight and mixed vaccines, including autogenous preparations of both kinds, this more rapid increase in sensitization is due to the increased ability of the patient to combat his infection. If anything, the mixed vaccine is more or less of a handicap, depending upon the number of different kinds of bacterial proteins entering into the mixture, and, by the same token, upon the multiplicity of the mixed infection against which it is employed.

However superior to straight vaccines for the production of the nonspecific tolerance in selected cases, the mixed vaccines are unquestionably less efficient as "specific" sensitizers, and are more dangerous under all circumstances in mixed infections. This is as should be expected, if the matter of the production of bacterial immunity is regarded rationally, from the point of view of the physiologic effects of remedial agents, here, for all practical purposes, two in number—the toxic portion and the nontoxic portion of the protein molecule—and is not viewed as the effect of a single agent, and more especially when "camouflaged" as *antibodies* produced by an *antigen*.

The gain in sensitization against the streptoprotein during the first series of injections was, as already stated, 10,000 units. This gain during the second series was over 40,000 units—much less comparatively than the gain against the tuberculoprotein during the same period and with the same treatment, but not under the same conditions. This gain, actually, should have been more, not only on account of the improved condition of the patient, and for the reason that the bacterial protein of this microorganism is a better sensitizer than that of the tubercle bacillus, but principally because the strepto infection was treated *specifically* during the second series of injections, the mixed vaccine containing streptoprotein. This was notthe case with the vaccine used in the first series of injections.

Other than stating that the streptoprotein has always proved a "mean" protein with which to work, and that streptococcic infections, at least when secondary to a concomitant tubercular infection in its early management, seem to be more safely and more satisfactorily treated by a nonspecific therapy, the only further explanation I shall offer for this failure of a greater increase in sensitization against this protein is that the focal phenomena, finally noticed with the mixed vaccine, acted as an inhibiting factor.

This was undoubtedly the case with the colon protein, against which the

initial degree of sensitization was not ascertained. The three weeks of colon protein injections of the mixed vaccine, however, increased sensitization against this protein about 30,000 units, which was a very small increase for the number of injections employed.

I am strengthened in my opinion that the focal phenomena are the principal factors here, not only from my observations of the sensitizing qualities of these two proteins with many other cases, but from their later behavior in this case. A very little later in his treatment this patient evidenced a focal tolerance of the colon protein, after only a few injections of this protein used as a straight vaccine, which equaled 200,000 units; while still a little later a focal tolerance was obtained with a few injections of the streptoprotein of 120,000 units. All of these injections, although causing systemic reactions, were devoid of any effects focally; but it is possible that their respective bacteria had then ceased to be focal factors, that, by this time, the mixed process had been converted into an unmixed tubercular infection.

This tenable conclusion would seem to be upheld by *the rapid improvement of this patient noted after the focal manifestations produced by the colon and streptoproteins had subsided.* This phenomenon has been often noted in other cases, after the initial stage of improvement, and with other bacterial proteins, including the tuberculoprotein particularly in infections of the joints.

With this case it was also ascertained that sensitization against the staphyloprotein had very perceptibly lessened at the end of twelve weeks; and that, with the colon protein, this was not the case at the end of eleven weeks. At the end of twelve months sensitization against the streptoprotein, although it had waned perceptibly, was still efficient for the production of a sharp reaction after an injection with that protein, which indicated it had lost nearly one-half. In this respect the tuberculoprotein is apparently in a class of its own; for, at the expiration of one year and six months, absolutely no evidence was apparent with this case that his sensitization against this protein was not as high as it had been at the conclusion of his treatment.

It required eighty-four weeks to sensitize this subject to the tuberculoprotein sufficiently for 2 c.c. not to cause a systemic reaction when given subcutaneously; thirty-two weeks to sensitize him against the streptoprotein so that 1.2 c.c. caused but mild systemic symptoms; twenty weeks for like but more toxic results from 2 c.c. colon protein—and the sensitizations against the two latter, and especially the colon protein, were undoubtedly delayed by untoward focal phenomena—while an equal degree of sensitization to that against the tuberculoprotein, the poorest sensitizing protein of them all, could have been obtained against the staphyloprotein, the best sensitizer, in probably six weeks at most.

The above relation as sensitizers, and as evincing the comparative virulence, of the above-named bacterial proteins has proved practically the same in every single one of some hundred cases where one or more of these bacteria have been found as concomitant infectors with the tubercle bacillus; and this fact alone furnishes the most potent of reasons against the employment of mixed vaccines that can possibly be advanced. This is not a haphazard conclusion, nor is it based alone on the behavior of these four different bacterial proteins upon the infected subject; for, although these differences are accentuated possibly

with the multiple infected, they absolutely obtain to a possibly less extent with the uninfected. Almost absolutely exact comparisons were possible with these protein preparations for the reason, as already given, that they each contain a like amount of their respective bacterial substance, of a multiple strain, to each cubic centimeter, of a like cellular fineness in suspension or solution.

As a sensitizer the polyvalent colon protein stands between the staphylo- and streptoprotein preparations, but much nearer the former than the latter. It is a good protein with which to work. As to the polyvalent streptoprotein, as has been said, it has proved so unexpectedly puzzling with which to work at times, that, in the more acute cases especially, if this protein is found to be specific to a concomitant infector, and the case is found not to react to some other, and less "aggressive," protein, it has been, and still is, my custom to deliberately sensitize against, preferably, the staphyloprotein, and employ this protein to control tolerance.

This process of sensitizing the subject to this protein preparation can be accomplished generally after three intravenous injections, followed by a wait of two weeks, when the former nontoxic initial sensitizing dose almost invariably causes the classical reaction when employed intravenously. This initial dose averages 0.1 c.c. After a few additional intravenous injections the patient will invariably begin to react to, of course, a much larger dose given subcutaneously. It may be added irrelevantly that this preparation, as well as the colon protein, has been doing yeoman service in the tropics for two years in the treatment, nonspecifically, of certain chronic skin affections, and of the so-called tropical ulcer, many of them of undiscovered etiology.

Additional evidence that this patient was being gradually and efficiently sensitized to the tuberculoprotein is found in the following two experiments. It had been found quite accidentally that when a subject would tolerate a certain dose of any of these bacterial protein preparations when given subcutaneously, and when this systemic tolerance of the protein was mostly due to sensitization, and not to a tolerance of the poison, that from 1/100 to 1/20 of that dose of the same protein could be given intravenously with safety, although it was followed by a chill. When this patient could tolerate 1 c.c. tuberculoprotein in the manner mentioned, and after a sufficient time had elapsed to allow any possible tolerance to wane, 0.025 c.c., or 1/40 of the nontoxic subcutaneous dose, was given intravenously. This was followed in a half-hour by a chill, and the classical reaction, in no way differing from that caused by any other protein. His degree of sensitization at that time was not sufficient to break up 0.025 c.c. of this particular protein beyond the toxic stage of its cleavage intravenously.

When, however, the patient could tolerate 2 c.c. of this protein subcutaneously this intravenous procedure was repeated, but with absolutely not the slightest noticeable reaction of any kind soever. Very obviously 0.025 c.c. tuberculoprotein could now be broken up beyond its toxic state of cleavage when introduced into the blood stream.

This exposition must not be considered as a model for the management, or even treatment, of the tubercular process, but rather as a skeleton upon which a model for each class of this infection of such varied manifestations might be partly constructed and finally built to fit the exigencies of each particular case.

This work was all completed over three years since, and has been reviewed and studied, written and rewritten, and compared with much of the more recent work, especially with that having to do with the nonspecific treatment, with proteins, of, for the most, chronic infections. I have attempted to reconcile my results with other conceptions of immunity at more or less variance with Vaughan's theory of protein sensitization, notably those of Jobling and Peterson, and Bronfenbrenner; but with results not complimentary to these other conceptions, mostly in that they are not reconcilable with two fundamentally important considerations—the patient and the remedial agent. The doubly, or multiply, infected organism finds no place in these schemes; and the double physiological effect of proteins is entirely overlooked.

If there are any flaws in the interpretations of the results herein set forth, which, with the exception of certain views on toxicity, are but the clinical application of Vaughan's experimental conclusions, a great deal of additional work with vaccines upon a variety of other infections done since has, so far, failed to make these evident. However, of this I am certain, of the two factors entering into the successful treatment of the infections, in so far as protein therapy alone is concerned, the nonspecific and the specific, the former is of the more importance, in that it paves the way, so to speak, for the more delicate procedure of specific therapy, *when this is necessary;* and with tuberculosis, for the consummation of the much more efficient, much more enduring, results of this therapy, a hypersensitization against the most aggressive infector of, in the great majority of instances, a multiple process, the tubercle bacillus.

I have been repeatedly asked why, when such good results so often follow a nonspecific therapy in tubercular infections, run the risks of the more dangerous administration of the homologous protein. The answer differs only in one respect from one of Gay's presumable reasons for preferring a specific to a nonspecific therapy in typhoid, which was that "*in addition* it will produce an active immunity." My answer always has been that the tuberculoprotein *only* will produce an active immunity; and it might be added that after the good results have been obtained from a nonspecific therapy, the specific therapy is no longer any more dangerous than the nonspecific. That it is the more efficient of the two, note the following:

After 24 weeks of treatment with proteins other than the tuberculoprotein, this patient had gained in sensitization against the latter about 6,000 units; but after only seven weeks of treatment with the tuberculoprotein his gain was very much over 44,000 units.

If there was any reason for having continued the tuberculoprotein in this case until 2 c.c. caused no perceptible reaction it was because it had required on an average of 2 c.c. of other proteins to control his tolerance at various times. This dose would represent 200,000 units; but how much beyond this figure his degree of sensitization really had reached I do not know; although, without much doubt, it was higher.

In the first place, from the time he was given 1 c.c., when he was receiving his injections once a week, only ten additional treatment injections of the tuberculoprotein were used, first at two-week intervals, and then at intervals of a month. From none of these injections was there ever any but a very mild

local reaction, and not always this; so that these might well have been due solely to some of the injected protein being deposited in areas of skin previously locally sensitized by one or more of his now many injections of this protein.

In the second place, eighteen months showed no abatement of his sensitization from a repetition of this dose; and, as stated this was verified by an intracutaneous injection of tuberculoprotein supplemented with a subcutaneous injection of a protein to which he did react, as well as by an intravenous injection of a former nontoxic dose of this protein. So that, rather than evincing an undiminished sensitization, these tests really demonstrated a sensitization not diminished to such an extent as to cause a toxic cleavage of a former nontoxic dose of the tuberculoprotein.

Two years after his discharge as cured, long before which time he had resumed his former occupation—in fact, he had done this several months before his discharge—this former pitiable object of humanity was the picture of perfect health, and, with the exception of a very perceptibly retracted right chest wall, and some healthy scars of the neck, bore absolutely no signs of his severe infection. Three years after, inquiries from an interested friend elicited the information that he was still a hard working, perfectly healthy man, with habits of life in marked contrast, for the better, with those of his pre-treatment days—and this has practically been the later histories of some twenty others, in so far as it has been possible to learn of these former advanced tubercular patients.

As to the blood, this case was unfortunately not among the number upon which counts were, at least regularly, made; nor, as will be seen, are the conclusions following based upon the actual number of cases where counts were made, so much as upon comparative counts made during the absence, with those made during the presence, of that nonspecific condition here designated as tolerance. The following tables are really based upon counts from 12 cases, 36 in number, and so divided that the two extremes, and the mean, changes in the small lymphocytes will show a fair average; and it is, let it be added, only very recently that these counts have been arranged for study, and certain deductions drawn therefrom, although they were all made several years since for a somewhat different purpose.

This purpose may be said to have had its inception in the observation of Friedberger and Schymanowski, cited by Vaughan,[7] that the presence of leukocytes seems to prevent the formation of *anaphylatoxin*, which, whatever its real matrix, is a *protein poison*, and that they apparently destroy it when abundantly formed. The suggestion of Vaughan that the leucocytes digest the poison and convert it into a harmless body, taken in conjunction with the noted leucocytosis early following the injection of proteins, seemed to offer a possible means of controlling injections given for the purpose of producing tolerance, and of maintaining it at efficiency; that is, of determining the intervals between treatment injections.

This opinion, as to the utility of the numerical white count, has now been broadened to the extent that the *blood picture* is considered of equal, if not greater, importance than the differential white count, and that this differential, if the smears are carefully and uniformly prepared, will show all that, or more than, will the numerical count, even to the extent of obviating the possible neces-

sity of making the latter; and, in that this picture offers a means of no mean order for treatment control, in that it probably offers very early evidence, not only of an ill-directed therapy, which is very desirable, but also of the progress of the patient at an earlier date than any other signs indicate. As to its offering any sure means of gauging injection intervals I am still somewhat in doubt.

First as to the blood picture, strictly speaking. Possibly due to the fact that my cases of tuberculosis have been, for the most, advanced ones, I was early struck by the difference in appearance of the white cells of some of the smears made for differential counting, and, in those few instances where they were made, by a certain difficulty in making numerical counts of blood from the same patients, when compared with other specimens. At that time this was at first thought to be due to faulty preparation of specimens, in that most of them were carried from the bedside to the laboratory for fixing, staining and examination. No account was taken of the fact that my office cases were mostly far along in convalescence, and furnished the good specimens, and that my bedridden cases were of particularly ugly types, and furnished the bad specimens; so that, this difference between the two classes was attributed to a possible drying out of the specimens before fixing.

The fixing of specimens at the bedside was easy of accomplishment; but this offered no solution. Before the institution of a portable microscope and staining outfit were well established, however, some of these specimens began to assume a different appearance. The white cells from those patients who were improving the more satisfactorily, or rather, from those who did so later on, were gradually assuming a fatter, more rotund, healthier appearance; were taking the stain better, could be more readily differentiated and, quite apart from their transitory increase following each injection, with the accompanying relative neutrophile increase, they were assuming an altered relation differentially in other respects, if really not a more gradual, more lasting, although less marked, increase numerically.

Counting the large mononuclears and the transitionals as large lymphocytes, and the eosinophiles and mast cells as polymorphonuclears, for the reason that this procedure, now recognized as at least unfortunate, greatly facilitated the making of many and repeated counts, the following table is submitted as showing the normal percentage of white cells according to this division; the approximate average of change from the normal with the advanced tuberculous process having one or more secondary infectors, and the effects, a more or less prompt alteration of this latter, produced by the injection of one or more beneficial doses of protein—that is, the average differential picture of the mixed tubercular subject with an inefficient tolerance, and that of the same patient after a more or less efficient tolerance has been established, in comparison with the normal picture.

The counts, the average results of which are portrayed in the third line of the table, it must be understood, were invariably made from two days to one week after any injection of the treatment protein; that is, after the transient leucocytosis immediately following the injection had subsided. For the purpose of making these counts, as has been said, was merely to regulate protein treatments.

	SMALL LYMPHS	LARGE LYMPHS	POLYMORPHS
Normal	22%	11%	67%
Inefficient tolerance	20%	16%	64%
Efficient tolerance	2%	24%	74%

From this table it can be seen that the low small lymphocyte count, invariably associated with correspondingly high large lymphocyte and neutrophile counts, may be said to constitute the most prominent characteristic picture of the early improving patient; and, when this occurs, or even when a tendency towards this changed numerical arrangement obtains and is accompanied by the improved physical appearance, if the term be permitted, of the cells, it can be regarded as infallible evidence that the effects of the protein injections are beneficial to the patient.

As to the promptness with which the maximum change in the small lymphocyte may occur, note the following: Among the half-dozen cases where zero was reached with respect to this cell, this was noted in one joint case with an initial 17 per cent after three injections given at three and four day intervals; while, in marked contrast, with another case, an ambulant pulmonary with an initial 24 per cent, this occurred only after thirty weeks of treatment, many protein injections, and after the ninth injection of the tuberculoprotein.

On the other hand, the highest low percentage of small lymphocytes noticed in a bed-ridden pulmonary, 16 per cent from an initial 24 per cent, was obtained only after the eighteenth injection of a protein other than the tuberculoprotein; while with another pulmonary, also under a strict regimen, a reduction from the initial 28 per cent to 9 per cent was noted after a single injection of a protein homologous to a secondary infector.

It is interesting as well as significant to note that with still another advanced pulmonary an excursion of temperature following an attack of indigestion, *not an exacerbation of the process*, be it understood, acted more efficiently than a dose of vaccine, or even than a large number of them, in that it further reduced an already reduced minimum 10 per cent to zero—probably the effect of an absolutely specific autovaccine "activated" by the intestinal irritation accompanying the indigestion. This case reacted focally to the colon protein, be it noted.

All of these cases had shown a tendency, more or less marked, towards the low small lymphocyte count from the very first, or first few injections of vaccines.

There seems to be nothing to indicate any specific action in this, other than that, while a return towards the differential average of "inefficient tolerance" seems to be immediate after too large or too frequently repeated injections of proteins which cause systemic reactions, but no focal manifestations, this is only less immediate after injections of vaccines which do cause focal manifestations in that the influence of these manifestations, which are here secondary specific phenomena, is not exerted as promptly after the injection as in the former case. In other words, the same focal phenomena making for the greater variation between morning and evening temperatures, already discussed, seems equally to make for the undoubtedly less satisfactory blood picture, including the partial differential of the second line of the above table. To what practical application this could be put remains to be worked out.

Let us consider this question from another viewpoint, at least in so far as the above division of white cells will permit, viz.:

	LYMPHOCYTES	LEUCOCYTES
Normal	33%	67%
Inefficient tolerance	36%	64%
Efficient tolerance	26%	74%

This table would seem to place the weight of evidence greatly in favor of the leucocytes as being at least the principal factors responsible for the production of the nonspecific beneficial condition of the infected organism here designated as tolerance.

Again, considering the above table from the point of view of the phagocytic action of the white cells, the following deductions are both interesting and instructive. The lymphocytes, if not constituting the *macrophages* of Metchnikoff, may be said to include these phagocytes, the large mononuclears. One function of these cells is certainly the digestion of the metabolic detritus of the organism. The leucocytes in reality are the *microphages* of this illustrious savant; and it is these cells that play the important role in bacterial infections.

Now, at the time when the destructive changes in the cells of the infected organism, and these would necessarily include the leucocytes, would naturally be considered the highest, during an active bacterial process, when, in other words, *tolerance is inefficient* the lymphocyte percentage is at its high mark, and the leucocyte at its low; while, at the time that these destructive changes, if not at their lowest, are at least less high, during a rest in, or a retrograde of, bacterial activity, *when tolerance is efficient*, the lymphocyte is at its lowest, and the leucocyte at its highest mark.

The exact figures are here immaterial, for they are necessarily of the most relative, and beside the point; it is the facts that count, and these are too obvious to be ignored.

There are other and quite tenable deductions to be drawn from these partial differential counts; but, lacking the percentages of especially the large mononuclears and the transitionals, as well as accurate simultaneous numerical counts, which were made on insufficiently numerous occasions, these would be open to criticism as being premature conclusions.

However, it may be said that in every instance where a numerical count was made in conjunction with either the above partial differential, or with the differential of wider scope, there was invariably a greater or lesser increase above the normal of the total number of white cells with the intolerant cases, and as invariably an increase of the same kind, perhaps uniformly higher, with the tolerant subjects—in no instance, however, nearly equaling the transitory increase early following the protein injection.

Further, it may be said that the increase in the intolerant cases seemed to bear a direct relation to the multiplicity of the mixed infection; while the increase in the tolerant subject undoubtedly bore a direct relation to *both the sharpness and the evanescence* of the reactions produced by the protein injections, which undoubtedly indicates a higher relative specificity of the proteins employed.

The tendency of this composite blood picture, however, was to early and quickly revert to the normal with the consummation of an efficient tolerance and the discontinuance of reaction producing doses of vaccine, and again to return to the "inefficient tolerance" picture if tolerance became inadequate, for any reason, or focal reaction producing injections were given. And this could and did occur a number of times with many cases, irrespective of the stage of the treatment—in other words, *this blood picture had absolutely nothing to do with the degree of sensitization acquired by the patient;* while the degree of sensitization, as already shown, had everything to do with the permanent cure, or the specific immunity, established.

The tubercular patient with a semiacute process and a readily demonstrated lesion, whether in the form of a more or less circumscribed pulmonary focus or another similar lesion, for obvious reasons is the ideal subject for the study of protein therapy, and of its effects in relation with the progress of the infection. Such a subject in which the symptoms of the malady are visualized as the primary effects upon the infected organism of the parenteral cleavage of bacterial proteins of an absolute specificity, and secondarily so through the effects of this cleavage upon the infecting microorganisms, or on the process, if it is considered as a living, increasing or active, or, decreasing or inactive, entity, is far superior to any test tube efforts aimed at such a study.

The symptoms of a protein therapy, both the reactions and the results, although necessarily regarded in exactly the same light, must in addition be viewed as the effects of probably relatively less specific proteins, but of proteins whose potential qualities have been enhanced by modifying them physically to a greater or less extent; that is, in that they have been rendered capable of a more ready cleavage and, up to a certain point in their cleavage, of a greater toxicity, as well as capable of more readily sensitizing the subject against the homologous protein of the bacterial invader.

There is absolutely no other construction to be put on the change in the proteins of the preparations so far successfully employed in vaccination—from the time of the first authentic employment by Jenner of the relatively less specific, less virulent, virus of cowpox in prophylactically vaccinating against smallpox, to the modification of the virulence of the pathogenic virus by animal passage, as practiced by Pasteur, down to the more recent "sensitization" of the bacteria, as first practiced by Besredka, and the distintegration of the bacterial cells by mechanical means—as tenable as that this change is due to the fact that the virus, or the bacterial cellular substance, so employed is, or has been rendered, less resistant than the infecting virus or pathogenic bacteria.

Whatever the ostensible purpose of the method of modifying the bacterial protein for therapeutic application, and this has been various, this one absolutely essential thing has been accomplished, whether the original one has or not—invariably the protein has been made more susceptible to cleavage by the parenteral enzymes; and the only exception as to its toxicity having been at the same time relatively increased, is to be found in the case of Vaughan's "cell residues," from which the poison, an integral part of the protein, and not a pre-formed toxic body, has been removed by disrupting the protein molecule chemically and extracting it with absolute alcohol, in which the poison is soluble.

As to the proper designation of this therapeutic agent, the following is submitted. As toxins and ferments, both undoubtedly substances of a like, or enzymotic, nature, are correctly included among the antigens, if, indeed, they do not wholly constitute this class of hypothetical bodies, then the sensitizing proteins *per se* may not be rationally so included, since the bodies formed against these substances, in the light of Vaughan's still unrefuted advancements, are themselves enzymotic in nature, and, unlike the antibodies, are not formed in the blood. Neither can the bodies formed against the sensitizing proteins be rationally termed antibodies, which are hypothetical substances of an antienzymotic nature.

As to one other so-called antibody, that of agglutination, Widal came to the undoubtedly correct conclusion several years since that this phenomenon was not a reaction of immunity, but a reaction of infection. Considering the agglutinable substance of the bacterial culture not as an essential part of the bacterial cell, which is undoubtedly a correct conclusion, but as a probable excretory product of the bacterium, just as the toxin is a secretory product, this agglutinogen might, by a certain possibly excusable laxity of the designatory sense, be included among the antigens; while the agglutinin might be regarded as an antibody, particularly as, like the antibodies, it seems to be formed in the blood, and in that it also has no bacteriolytic action.

Need it be stated here that any bacteriolytic action attributed to the antibodies, antitoxin, like so many other Teutonic emanations, scientific and otherwise, has been almost entirely taken for granted! Indeed, the weight of evidence seems to be much in favor of the antibodies being specifically and indirectly responsible for the production of a nonspecific immunity in infections caused by toxin producing bacteria through tolerance—not by enhancing this condition, but by reducing the amount of poison being liberated in the infected organism, through neutralizing the toxin whose cleavage action on the body cells is producing it, to a point below the tolerance of the subject, thus rendering tolerance efficient.

As far back as 1902 it was demonstrated in Vaughan's laboratory[8] that immune serum, serum from the sensitized animal, had no bacteriolytic action not also possessed by normal serum, despite the fact that the immune serum contained abundant "antibodies"—possessed high powers of agglutinating the homologous bacteria. Yet, without exception, the critics of the theory of protein sensitization still cite the fact that no specific proteolytic action can be demonstrated in blood serum as more or less conclusive evidence that there are no such bodies as specific proteolytic enzymes. The extreme probability that it was this early recognized lack of evidence of the presence of such ferments in the serum, coupled with overwhelming evidence of their existence elsewhere parenterally, which was more or less responsible for Vaughan's theory as it stands, and has stood, since its promulgation, seems to be entirely overlooked.

The theory of protein sensitization, be it understood, was not evolved to explain the mechanism of anaphylactic shock, but to explain immunity; and, although it was tentatively considered by its author as offering a possible explanation of this dreaded experimental phenomenon, it has not been materially affected by any subsequent work—the sensitized animal is particularly liable to

shock, whether it is produced specifically or nonspecifically, and the protein poison must still be rated as at least one of the *substances dechainantes* of our French confrères.

Let us consider more closely, and as fair samples, the two criticisms of Vaughan's theory of immunity which have already been cited, as to what weight, if any, they should have in refuting his advancements.

Jobling and Peterson[9] assume that bacteria are lipoidal in nature, and believe that bacteriolysis is due to the lipolytic effect of the blood serum, the bacterial protein then going into solution. And, as they explain the toxicity of both the injection and reinjection of protein by its adsorption of serum antiferment, with a consequent toxic autodigestion of serum protein, and state that an increased resistance to digestion is conferred on the protein of the injection thereby, sensitization, according to this view, can be considered only as an increased ability of the blood to digest itself in the presence of the homologous protein of the injection, which latter is itself protected from destruction by the same process. It may be added that a protein in solution is still a protein, and must be taken care of whether for the purpose of nourishment or for that of elimination.

Much work in Vaughan's laboratory,[10] done years before this, had demonstrated that bacteria are essentially protein in nature, and that fats and waxes make no part of this protein; while work in the same laboratory had early established that the cell residues either sensitize without increasing the capability of the serum antiferment to be adsorbed, or were nontoxic with this adsorption.

Bronfenbrenner,[11] on the other hand, assumes that the specific ferment of Vaughan circulates in the blood stream. He regards sensitization as a specific phenomenon, but considers that its specificity rests not in the ferment, but in the mode of its activation. The treatment injection of protein causes the production of antibodies in the sense of Ehrlich. These specific antibodies unite with the antigen of the reinjection, which causes a radical change in the degree of dispersion of the serum colloids, and the normal, nonspecific serum ferment is activated thereby. Toxic symptoms occur only when this ferment acts upon the proteins of the blood, which it does after large reinjections. When the reinjection of antigen is small, it is digested, but without symptoms of intoxication. These visible signs of intoxication mark the *anaphylactic* animal; while the invisible signs of toxicity mark the *immune* animal—in other words, immunity is the result of what might be called a misdirected anaphylactic shock.

This theory, its author states, explains the phenomenon of the parenteral digestion of proteins, as well as the mechanism of *immunity*, on a basis very similar to that of Vaughan; but nothing could well be farther from the fact. Its most glaring difference lies in its inconsistencies, such as a specific *anaphylaxis* and a nonspecific *antianaphylaxis*, which latter is also considered as a benign condition. Saying nothing regarding the assumption about the specific ferment, this theory does not even stand the test of the behavior of, again, the cell residue of Vaughan, which sensitizes and so, according to this conception, must produce antibodies. Beyond this, however, these "antibodies" fail to function, for the sensitizing "antigen," reinjected in whatever dose, fails to produce toxic symptoms; although it will cause harm to the infected subject without

causing visible signs of injury upon its injection, while its homologous protein may cause great benefit while evincing very marked signs of toxicity.

In effect, as far as the question of immunity is concerned, the methods employed in arriving at the conclusions of the above two citations are "empirical." Two absolutely well defined and powerful therapeutic agents, which have dissimilar primary effects and somewhat similar secondary effects, are regarded as one single agent; and this is done inconsistently for the reason that, in both instances, the possibility of separating toxic proteins into their two essential component parts, the toxic nonsensitizing and the nontoxic sensitizing, is acknowledged. And, to quote Fischer,[12] *"while we may not despise any good therapeutic procedure just because it is empirical, we have every reason to despise the modern therapist who employs the empirical method where a rational one is at hand."* The above methods are not rational.

As before stated, the ultimate test of any theory of immunity must rest with its clinical application; and in this respect Vaughan's theory is found far from wanting in comparison with others. In the preface of his "Protein Split Products" this authority makes certain brief statements of points dwelt upon in the volume. Some of these points will be given in conclusion as having been verified clinically with several hundreds of cases of different infections, treated nonspecifically and specifically with different protein substances, from among which the case cited and discussed has been chosen, not for the reason that it is unique as far as evidencing the correctness of these points is concerned, but rather because the patient's amiable attitude towards any possible discomfort due to testing out questionable conclusions allowed these tests to be made in greater number than with any other single case.

Protein sensitization and bacterial immunity, apparently antipodal, are in reality identical.

Vaccines are protein sensitizers.

When proteins are subjected to the action of disrupting agents, as when introduced parenterally, *there is the possibility of the chemical nucleus being set free more or less completely, and to the extent that it is detached it becomes a poison.*

The protein poison is not specific.

The tolerance which may be secured by the protein poison is not specific.

The sensitization developed by a protein is specific, but is not due to the poisonous group of the protein.

The poison elaborated in all infectious diseases is the same.

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PNEUMONIA AND MENINGITIS*

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ALL infectious diseases are potential producers of "carriers." We mean by that that a germ which produces a disease may outlive the symptoms of the disease in the individual and may remain living and reproducing in the body of its host from whom it is given off or excreted. The individual in whom such bacteria live and from whom they are given off we call a carrier. To account for this state of affairs, in which a pathogenic organism thrives within the body of a host, we say that the host has become immune to the organism and that the organism has at the same time become immune to the host,—to its cells and fluids. Between the two organisms there has been developed a reciprocity that permits both to live harmoniously. If, however, these symbiotic bacteria leave the body of their host and gain access to the body of another individual, disease is apt to occur in that second individual.

Sometimes, however a carrier is a person who has not had the disease which his bacterial guest is prone to produce. Such a person is oftentime only relatively immune and any shock may make it possible for the guest to rob the house and even to destroy the host. Shocks which are active in lowering resistance may be such relatively slight things as mild fatigue or chilling.

So there are two types of peace between organisms,—between host and guest,—one, that which follows a struggle; the other, that which seems to be the result of a temporary agreement. The former tends to be more permanent; the latter to be less so, or even very transient. In the case of typhoid the peace is apparently permanent, as it is in scarlet fever. In the case of pneumonia, on the other hand, it is apt to be transient and in force only during the good behavior of the individual. In meningitis, the conditions we do not understand even as well as we do those in pneumonia. If there is a truce between meningococci and host, then those cocci act as do the Huns, striking with no apparent good reason.

It is sometimes believed that the germs of carrier origin are less virulent than those excreted by persons sick of a disease and that transmission from person to person heightens their pathogenicity. So one accounts for the fact observed in many epidemics that the early cases are more benign than those appearing later in the epidemic. In the cases of meningitis and pneumonia, at least, there seems to be no good evidence that this is true. Or, if it be true, then there is evidence in the course of events as we have seen it in Camp Greene, that transmission from person to person did not occur, for in neither pneumonia nor meningitis was there any evidence that the virulence of the organisms was enhanced.

Naturally enough we know most about the carriers of those diseases in

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which the causative organisms are known. Also where our knowledge of the bacterium concerned in a disease is most complete, there also is our knowledge of the carrier problem most complete. For instance, we know a great deal about the carrier problems connected with typhoid fever and diphtheria. We know less about those connected with meningitis and pneumonia, and next to nothing about those pertaining to mumps, scarlet fever, and measles. From this it follows that the methods we pursue with regard to typhoid fever are based upon knowledge and are therefore systematic, while with regard to pneumonia and meningitis the methods are based upon very incomplete knowledge and are therefore unsystematic and empiric. Just because of this lack of definite knowledge of meningitis and pneumonia it seems interesting to see what can be added to our understanding of it from our experience in this camp and to compare our experience with those in other places where soldiers are gathered together.

These two diseases have been prevalent in the camps and contonments of the United States during the past winter and have been the basis of a great deal of comment both lay and professional. Meningitis particularly has had an intense sentimental effect. Sometimes this was really merited, sometimes not. Unfortunately, a great deal of the excitement which has been an outgrowth of the incidence of both diseases has been due to a sort of general false impression fostered by unfounded individual and unscientific deductions. Not in all cases, of course, but in many. There has been too much of what "my boy says;" too much correspondence by "my boy" on themes which he should never have tackled. He didn't mean to cause trouble, but he did, and it can scarcely be prevented. We have a democratic army and every one outside, and inside too for that matter, thinks he has a perfect right to draw his own conclusions and criticize when and how he pleases. Often it happens that he does not know the whole situation and more often he is not fitted to discuss the situation even if he knows it. A great many persons have been unable to realize that under the very unusual weather conditions which prevailed during the past winter the only wonder is that there was so little sickness in the camps; not that there was so much. By all the usual rules and suspicions meningitis and pneumonia should have been far more widespread than they were. Measles complications might have run riot. That this did not happen at Camp Greene was due largely to the Base Hospital, a most unusual institution, which in spite of its youth has been extraordinarily efficient.

Suppose we leave these glittering generalities and get down to cases, considering for the moment pneumonia.

There are two types of pneumonia that give us trouble, lobar and lobular. The latter, especially under camp conditions, is a bronchopneumonia. In Camp Greene during November and December there were but seven cases of bronchopneumonia on register cards, all of them in December. At the same time there were forty-one cases of lobar pneumonia, none of them complicated. In January there was but one register card with the diagnosis bronchopneumonia on it. There were, however, several cases of empyema, suppurative bronchitis with empyema, and suppurative bronchitis with bronchopneumonia, all of which were probably originally cases of bronchopneumonia with complications which masked

the primary condition. In January there were register cards for 156 cases of lobar pneumonia, eight of them complicated. One of the complicated cases is of unusual interest because in it the pneumonia was associated with an acute general peritonitis not of intestinal origin. The combination suggests a primary pneumococcus septicemia with secondary attack upon the lungs and peritoneum.

If we study the records for complicating pneumonias we find an opposite state of affairs, in that here the bronchopneumonias predominate over the lobar. For instance, take measles. In November there were no pulmonary complications. In December there was twenty-one, one a bronchopneumonia. In January, measles was complicated in 55 cases, in 13 of which there was a bronchopneumonia.

These complicating pneumonias are most commonly due to streptococci and are the ones which are most apt to be associated with empyema. Personally I feel that when empyema appears in measles, there is a pneumonic process underneath the pleura—that a bronchopneumonia has preceded the appearance of pus in the pleural cavity. The data would be interpreted to mean that of fifty-five cases of complicated measles a streptococcic bronchopneumonia appeared in twenty. It may also be that some of the cases diagnosed lobar pneumonia were in reality bronchopneumonias. This is quite possible because in not a few cases the lobular consolidation is so diffuse that the physical findings approximate those of lobar pneumonia.

Irons and Marine (Jour. Am. Med. Assn., 1918, lxx, 687) call attention to the fact that the physical findings were misleading until an exploratory needle showed that the dullness, thought to be due to lobar consolidation in some of their cases, was really due to the presence of an exudate in which streptococci were found. Also I know from observation at the Base Hospital and from Captain Placak that some, at least, of the cases diagnosed lobar pneumonia were found at autopsy to be massive, or better, diffuse, lobular pneumonias. These are sometimes called pseudolobar pneumonias.

Now because these lobular pneumonias are complications or sequels of other diseases, and since it is only the lobar type that occurs in epidemics, it is the lobar type about which a large amount of work has centered. When we speak of the pneumonia problem in a community me mean lobar pneumonia.

For many years a group of men, particularly in the Rockefeller Institute, have devoted themselves largely to a study of pneumonia. From their researches a valuable mass of facts has accumulated, most of which in condensed form is available in Monograph 7 of the Institute. Among other things these workers have done, has been to show, by means of immunity reactions that there are four main types of pneumococci which they call Type I, Type II, Type III and Type IV. By bacteriologic studies of large numbers of cases of pneumonia they have shown that,—

	Type I	is	present	in	33%	of	the	cases
	Type II	"	"	"	33.5%	"	"	"
	Type III	"	"	"	13%	"	"	"
and	Type IV	"	"	"	20%	"	"	"

They also have shown that Types I and II are responsible for the most

malignant forms of pneumonia and also that they are the least common inhabitants of the mouths of healthy persons. For instance,—

Type I	occurred in	0.8%	of healthy	mouths		
Type II	"	" 18.2%	"	"	"	
Type III	"	" 28%	"	"	"	
Type IV	"	" 52.9%	"	"	"	

In other words, Types I and II which account for over 66 per cent of the cases of pneumonia are present in but 19 per cent of healthy mouths, while Types III and IV which cause about 33 per cent of the cases of pneumonia are found in 81 per cent of healthy mouths. These data were derived from bacteriologic examination of 297 mouths of healthy persons, 116 of which were infected with one or another type of pneumococci.

If one is willing to accept these figures, then the logical thing to do in waging war on pneumonia is to guard against the carriers of Types I and II, by discovering them bacteriologically and isolating them until they are free. Also since these types are very commonly found in the environment of patients suffering with pneumonia of a severe character, these patients should be treated just as they would be were they suffering from any other sort of infectious disease, i. e., by isolation and by antiseptic methods applied to the patients and to the objects in their immediate environment.

Now very obviously such a method of dealing with pneumonia, while it can readily be applied to patients in hospitals and to small groups of persons, can not so readily be applied to large bodies such as we find in our camps and cantonments. Nevertheless something like it has been done in England, where, according to Evans (New York Med. Jour., Feb. 2, 1918, p. 220) they make a bacteriologic examination of all recruits, of all patients, and of all contacts; isolate all those found infected, and sterilize all infected mouths. In following such a plan there are chances of error of course. Cases in which infection is localized in the nasal passages where the swabs can not be introduced will be missed. And then also, if the statistics of the Rockefeller Institute are correct, something like 116 men out of 297 would have to be isolated during disinfection for pneumococci alone. How many more would have to be treated in the same way for meningococci we can not say. Or if we should only attempt to disinfect carriers of only Types I and II, then two-thirds of the 116 cases would be concerned. This limitation to these two groups would however not be safe for Miller at Camp Dodge, (Jour. Am. Med Assn., February 23, 1918, p. 564) had not a single death from patients infected with Type I, and the majority of his cases harbored Types II and IV. And there you are! If you try to collect the various experiences reported from the different camps, you apparently have to conclude to isolate and disinfect all carriers of pneumococci if you wish to play safe. Personally I believe, in the exigencies of the general situation that it were better to treat *all* recruits in the same simple way. By that means we would learn less about pneumococci types, but the important thing to do, as Vaughan has said is to prevent pneumonia. We are running an army, and not a research institute, and what research we do is a side issue for the time being. I should send all recruits to a camp where for a certain period they would start

their training, and during that time I should attempt to disinfect as thoroughly as possible the upper respiratory passages without regard to the types of bacteria in them. Such a method is in use in our Casual Camp No. 1, and it seems to be effective. The results of the practice are not clear, however, because the general conditions are good. The reports seem to show that there is less pneumonia in the Casual Camp than in the whole camp. Also measles and mumps which in the Casual Camp appeared in contacts from other camps, seem to be declining more rapidly than in the rest of Camp Greene. All this may be an artefact, but it is suggestive, and points to the tentative conclusion that in attacking the pneumococci and meningococci in the nasal passages all the infections of the upper respiratory tract are diminished.

The mere presence of pneumococci in a nose or throat is of course not the whole story. There are many persons who harbor them for long periods of time without discomfort. Invasion and pneumonia depend upon the relative resistance of host and parasite. Factors which produce such decreases of resistance are fatigue due to whatever cause, chilling, and the like. Also a person may be relatively immune to his own nasal menagerie and not to that of another person. He may harbor one type and acquire a second, and the two together, or the second alone, may produce disease. Such secondary infections (co-operating infections) may be frequent in pneumonia. When a primary pneumococcus infection is complicated by a streptococcus infection, the results are yet more severe. Under such conditions it were best to attempt in prophylaxis to limit the number of types of organisms, and so prevent mixed infections. Every man should live only with his own flora. (That holds in many social directions.)

The pneumonia problem of the camps has not been one concerned only with pneumococci, for if we take the reports of Cecil and Sackett (Jour. Am. Med. Assn., 1918, lxx, 728), and of Irons and Marine, we are led to believe that the streptococci must have played an exceedingly important role, not only in the group of primary pneumonias, but also in the measles-pneumonia, and pneumonia-empyema groups. For instance, in Cecil's series of pneumonias 67.7 per cent were due to pneumococci, 24.7 per cent to streptococci, 2.2 per cent to B. influenzæ and 5.4 per cent to the M. catarrhalis. Of the streptococcus cases, 24 per cent were of the hemolytic type. The mortality in streptococcus cases was over 30 per cent. The general mortality for pneumonia was 15 per cent. Empyema occurred in 12.9 per cent of the pneumococcus cases; in 24.9 per cent of the streptococcus cases.

Hackett, speaking of measles in Camp Upton, says that this disease was complicated by pneumonia in 35 per cent of the cases, and that streptococci were responsible for 17.6 per cent of the complications. At Camp Custer, according to Irons and Marine, many of the pneumonias were of streptococcic origin, therefore frequently lobular in type, and frequently complicated by empyema. They examined sputa for pneumococci and found none which agglutinated with sera of Types I, II, or III. During the period of acute respiratory infections, large numbers of throat cultures were made and 70 per cent of the men examined showed hemolytic streptococci, which showed a wide distribu-

tion of these organisms even in apparently healthy soldiers. Irons and Marine say that their "experience with these streptococcal infections suggests that while

	Nov.	Dec.	Jan.
Bronchitis, acute catarrhal	41	231	132
Bronchitis, acute suppurative	1	6	6
Bronchitis, ac. supp. with pneumothorax			1
" " " " lobar pneumonia			1
" " " " empyema and pericarditis			1
" " " " bronchopneumonia			1
Bronchitis, chronic catarrhal			3
Bronchopneumonia		7	1
Lobar pneumonia	7	34	148
" " with empyema			4
" " " otitis media			2
" " " ac. general peritonitis			1
" " " ac. meningitis			1
Empyema			3
" with pericarditis			1
Laryngitis, acute	4	92	32
Pharyngitis, acute	8	21	15
Influenza	9	197	171
Tonsillitis	71	139	152
Peritonsillar abscess	1	4	10
Vincent's angina	1	1	3
Rhinitis, acute	4	7	8
Otitis media	1	13	23
Sinusitis, ethmoiditis, mastoiditis	2	5	13
Totals	150	847	660
Measles, uncomplicated	82	293	450
Measles, complicated by—			
Acute bronchitis or rhinitis	2		
Influenza	1	1	1
Bronchitis, ac. suppurative	1	2	6
" " " and bronchopneumonia	0	1	3
" " " " empyema	0	1	5
" " " " empyema and influenza	0	2	0
Bronchopneumonia	0	0	3
Empyema and bronchopneumonia	0	0	7
Pyopneumothorax	0	0	1
Lobar pneumonia	0	0	2
Otitis media	0	0	10
Tonsillitis	0	0	12
Sinusitis, mastoiditis, ethmoiditis	0	0	2
Empyema, supp. bronchitis, otitis media	0	0	1
Pleuritis, acute fibrinous	0	0	1
Pulmonary tuberculosis, purulent pericarditis	0	0	1
Totals	85	314	505
Pleuritis, acute	4	11	21
Rheumatism, acute	8	20	20
Totals	12	31	41

measles is an important predisposing factor, other infections, as bronchitis, tonsillitis, diphtheria, and other conditions such as exposure, and excessive fatigue must be included—in short anything that may reduce resistance to infection by an organism quite generally distributed during the epidemic of colds and bronchitis; in the noses and throats of the apparently healthy as well as the sick."

These data show distinctly that the prophylactic attack on pneumonia must

not be limited to the pneumococci. At Camp Greene the records indicate in a very suspicious manner that the pneumococci were not all-important or even exceedingly important. By going over the register cards at the Base Hospital I have been able to collect the following data which are of some considerable interest, with respect to the probable types of infection in the respiratory disease. The months of November, December, and January only are given, because in the first place I was interested in collecting data from the early part of the period during which the respiratory diseases rose, and comparing it with the later periods, and secondly because the later files are not complete. Even as it is, there are numerous instances in which the cards for December and January are not completed. The figures are therefore not exact, though they are nearly enough so to indicate the trend of events.

These figures boiled down show that the acute infections of the respiratory tract were fewer in number in January than in December, except in the cases of pneumonia, and tonsillitis. Measles increased by about 62 per cent in January (over December), and was complicated in 10 per cent as against about 6 per cent in December. In November there were no cases of measles complicated by empyema. In December there were six. In January there were fourteen. In November three cases of measles developed complications, none of them severe. In December, twenty-one cases were severely complicated. In January, there were fifty-five complicated cases. In January, the number of pneumonia cases showed a marked increase both in uncomplicated and complicated cases. Also in January the number of primary empyema cases and of acute pleuritis rose.

These data taken together seem to indicate that in November and December, the respiratory infections were preeminently confined to the upper tract, and that later, in January, they had extended to the lower passages. There can be no doubt in the mind of the observer that the bronchitides became chronic, though the hospital records do not show it. From this the suggestion arises that the lower respiratory tracts of many of the men had lost their normal powers of resistance, and that a new acute infection,—such, for instance, that of measles or lobar pneumonia,—produced not only its proper effects, but also gave opportunity for an acute attack by the agent causing the chronic one.

It seems, therefore, from a study covering three months of respiratory disease, that the time at which to begin the prophylactic attack upon the complications of measles is prior to the time when respiratory infections have become chronic.

MENINGITIS

Pneumonia is the real menace of camps. Meningitis however is apt to inspire more fear, and when it becomes actually epidemic there is justification for this. When, however, it appears only sporadically, as it has in Camp Greene during the past winter, it is relatively a minor affair, especially when one compares it with pneumonia and measles, the latter with its complications. Mink (Jour. Am. Med. Assn., Feb. 23, 1918, p. 563) says, "Were it not for the fact that meningitis has always been held to be a serious disease, it would probably not inspire so great consideration." So long as such a belief does not interfere with our efforts to maintain the disease as a sporadic one it may be justi-

fied, but if it tends in the direction of neglecting measures for prevention, then certainly it is pernicious. It must be kept continually before our eyes that as a rule, the mortality from meningitis is much higher than from pneumonia, especially in untreated cases, and that even in treated cases it is somewhat higher. In a series of 712 cases noted by Flexner, the mortality was 31.4 per cent, just about what it has been in our series in this camp. In untreated cases the death rate may be as high as 85 per cent. In Dopter's series of treated cases the mortality was something over 16 per cent.*

From the standpoint of the carrier, meningitis is simpler than pneumonia, one reason being that there are fewer persons who harbor the organism. Another reason is that chronic carriers are less common than in either pneumonia or typhoid. The meningococcus seems to show a more marked tendency to disappear spontaneously. Also, different from typhoid and dysentery, the meningococci are not carried, so far as we know, by the hands, or clothing, or by flies or other insects. They are present only in the secretions of the upper respiratory passages, and not in the urine or feces. There is no good evidence that they can live outside the body for any considerable period of time.

One wonders just how many carriers there really are. In certain small groups of persons there may be as many as 70 per cent. On the other hand, in large bodies of men, there may be none. The figure obtained from 4446 examinations in Camp Greene was approximately 0.4 per cent. The technic used by the officers who made these examinations was technically perfect and above suspicion. Medlar (Jour. Am. Med. Assn., Feb. 16, 1918, p. 458) has shown that the number of carriers vary in different months. In November and December, 1917, for instance, he found from 3 to 6 per cent. In January, 1918, the number increased to from 12 to 20 per cent, in 3,000 cultures. What makes the difference? Is it methods of laboratory diagnosis? One is inclined to believe this in some cases. It is, however, more reasonable to believe that it is due to the closer physical association which comes with bad climatic conditions, and the coincidental bad housing conditions. With men huddled together in their tents, or in badly ventilated barracks, every chance is given for transfer of bacteria from one to another.

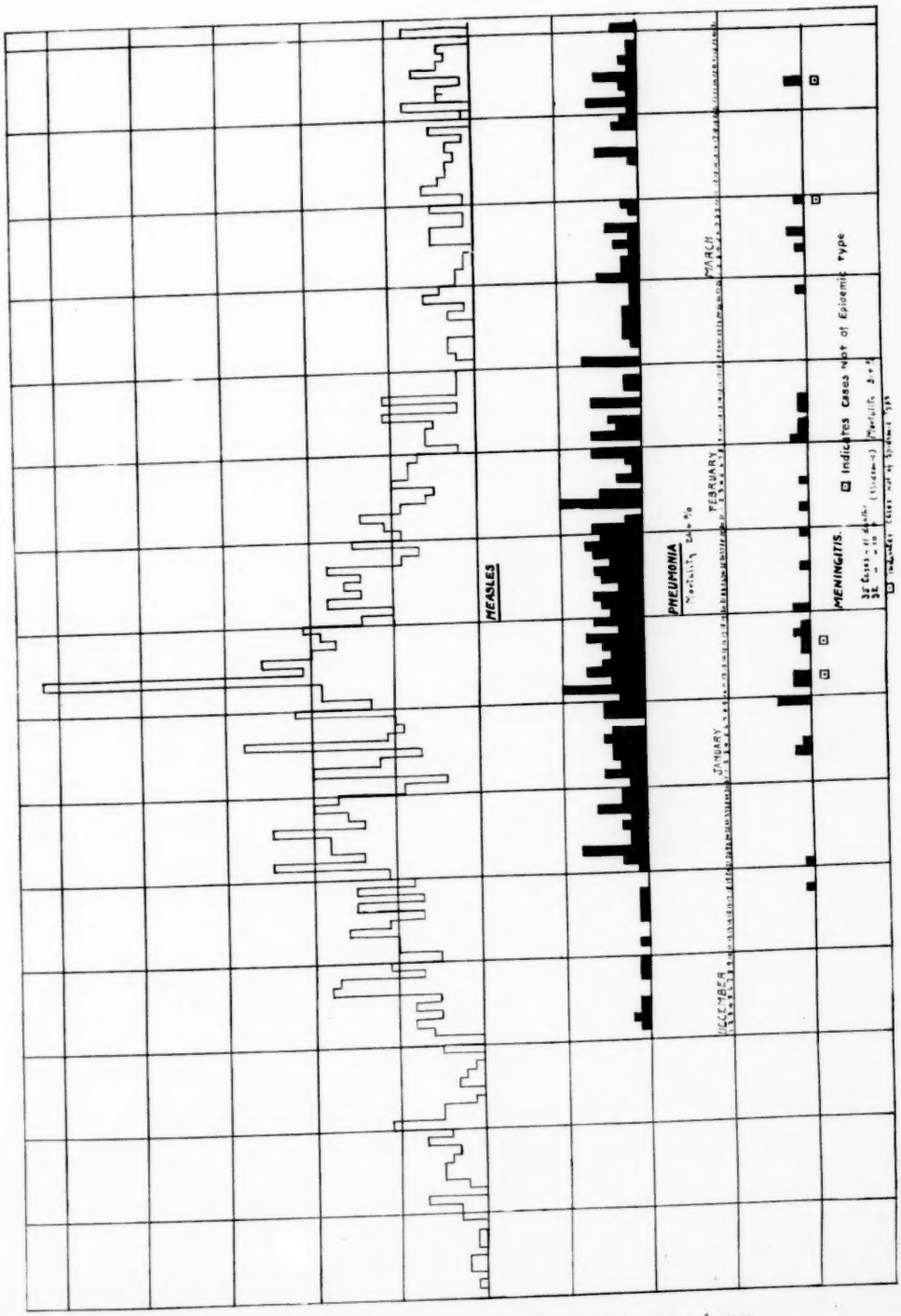
And yet Mink's statements are very disturbing to such a simple conception. For instance, he says that no cases of meningitis appear among the groups of "incoming recruits," notwithstanding the fact that these men were housed together, separated from the rest of the camp, for from twenty-one to thirty days, and despite the fact that there were large numbers of carriers among them,—sometimes as many as 25 per cent (by culture). Accordingly Mink believes that it is not the barracks life *per se*, nor the presence of carriers *per se* that gives the essential conditions for the appearance of the disease. He calls attention to the fact that after the period of detention the recruits were sent to duty and thereafter they enjoyed all the usual liberties, such as visiting the Y. M. C. A.'s and other places of entertainment. It was after this that the disease appeared, but even then the incidences of the disease and of the carriers did not correspond. In some barracks in which there were 25-30 per cent of

*Rosenow has recently reported (Jour. Am. Med. Assn., 1918, lxx, 759) a series of pneumonias treated with his vaccine. Among these cases the death rate was but 7 per cent.

carriers there was no meningitis; in others, with 8-9 per cent, the disease showed itself. Yet, in the whole series of cases in the command, the incidence of disease was higher in the carrier group than in those who were not carriers,—a state of affairs completely at variance with the rule. Small wonder that Mink is not impressed by the attempts to control meningitis by the methods based upon carriers! As a matter of fact the mere isolation of carriers seems to have had little to do with the control of meningitis in Camp Greene. So long as the effort was made only to discover and isolate carriers, without at the same time doing anything else, the disease kept reappearing. But in those organizations in which attention was paid as much to cleansing the nasopharynx, as to isolation of contacts and carriers, the disease disappeared. The facts may be the results of coincidence, but they are exceedingly suggestive. So suggestive is it to me that I am almost willing to say that the conditions could have been met and controlled just as successfully if the immediate contacts had been isolated in their own squad tents until they were cultured, and then if they were negative, allowed to drill and take part in all the routine duties of their organizations. At the same time the use of disinfecting sprays should have been used on all members of the company in which the meningitis appeared. I feel that the carrier is a source of considerable danger only when the men of an organization are low in resistance, brought about by fatigue, the result of overexertion or exposure. The men must suffer frequently from fatigue. Therefore the problem seems to center itself upon disinfection of the nasopharynx—the dwelling place of the meningococcus.

It is a fact that up to the present time the local causes of epidemics of meningitis have been sought in vain. Water, milk, food, all have been excluded from consideration. Moreover, as Frost says, the disease "does not present epidemiologic characteristics which we are accustomed to associate with a contagious disease. Even in carefully studied epidemics it is the exception rather than the rule to find any direct or even traceable indirect contact between successive cases." In Camp Greene there has been but a single case in which suspicion of contact could be discovered. Also, "it is unusual to find more than one case of the disease in a family, and when multiple cases do occur in the same house, they often occur so close together, or separated by such a long interval as to make it seem unlikely that one was infected from the other." In the Camp Greene series of cases the same statement can be applied to perfection. In a single instance more than one member of a company was attacked by meningitis, and in no case did more than one case appear in the same tent. These facts render it virtually certain that "direct contact with the sick is neither a necessary, nor even a very common factor, in contracting the infection."

The experience of Mink in regard to the progress of his epidemic of meningitis is strikingly similar to ours in Camp Greene. Mink says that the first thing in the sequence was an outbreak of coughs and colds so extensive that almost whole regiments were crippled with bronchitis, coryza and influenza. Four days later, the first case of meningitis appeared. So long as these respiratory difficulties persisted, meningitis did also, and finally when bronchitis and influenza subsided, so also did meningitis. I have not been able to get concise data on conditions as they existed in November during which two cases of



Daily incidence curves of disease in Camp Greene. 1 square = 1 case.

meningitis appeared, but the conditions since that time appear to simulate those of Mink. The chart shows graphically the number of cases of meningitis, pneumonia, and measles, by days, during December, 1917, and January, February and March, 1918, and demonstrates very clearly, it seems to me, the heaping up of these diseases during January, a month in which living conditions were at their worst. It was these months also in which the complications of measles and pneumonia were so frequent. (See table.) In this connection Frost says, (Public Health Reports, No. 26, 1913) "the seasonal prevalence (of meningitis) is strikingly similar to that of pneumonia and influenza, and not unlike that of a number of other diseases, (scarlet fever, measles, diphtheria and smallpox) in which the primary seat of infection is believed to be the respiratory tract." If this be true that the incidence of meningitis and that of the commoner respiratory diseases are parallel; if, in fact, the appearance of meningitis follows the rise in acute respiratory diseases, then one may quite reasonably draw the inference that there is some definite connection between the two. Medlar believes that meningitis is primarily a nasopharyngitis. One interpretation of that is that a nasopharyngitis of nonspecific character offers the opportunity for penetration of the mucous membranes by meningococci. It is a well-known fact of general pathologic interest that an inflamed mucous membrane offers special inducements to bacteria to pass through it. One reason for this is that there are increased numbers of phagocytes present upon inflamed surfaces, and these engulf microorganisms and carry them inward. Another reason is that the mucous membranes are colloidal structures which when swollen are more dilute and have less than a normal viscosity. Under such circumstances any particle may pass through them more readily than while they retain their normal water content.

It deserves mention that it seems probable that epidemic meningitis is not primarily an inflammation of the meninges, but is a septicemia in which the bacteria tend to become localized in the membranes of the brain and cord. This conception has been emphasized by Herrick in his remarks on meningitis at Camp Jackson (Jour. Am. Med. Assn., Jan. 26, 1918, p. 229). This is what might be expected from the clinical picture, especially in the fulminating cases, and from a consideration of the course the cocci would have to take to reach the meninges. That the bacteria must frequently be present in large numbers, and at a very early stage, in the blood is tested by the very early appearance of the petechial eruption from which the term *spotted fever* comes.

In conclusion, all that seems possible to say with regard to pneumonia and meningitis prophylaxis, is that both are due to invasion of bacteria which are inhabitants of the upper respiratory tract, that the conditions under which they become more or less widespread or epidemic are not understood, and that the only method for preventing their spread is to apply antiseptic methods to the mouth and nasopharynx. It seems obvious that the application of such methods should be put into practice in advance of the season of the year during which the incidence of respiratory diseases rises.

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ON THE RELATION OF PEPTONE TO BIOLOGICAL REACTIONS*

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WITH the outbreak of the war and the consequent curtailment of the supply of Witte's peptone, the question of the production of potent diphtheria toxin became acute. American peptones already on the market, while satisfactory for the production of tetanus toxin and allowing a profuse growth of B. diphtheriæ, did not give a satisfactory toxin production. Other American peptones were soon available which gave a diphtheria toxin of low potency.

Of the most of the American peptones one lot might give a toxin of 400 to 600 M.L.D. per mil, while the next lot might give no toxin at all. Within the last year and a half one of these peptones, however, has given fairly constant results.

A peptone was made up as nearly as possible of the same composition as Witte's peptone, with some variation, however, which there was reason to believe would make it a better peptone than Witte's. Toxin was produced with this peptone, using as comparison Witte's peptone and American brands. In all cases the new peptone gave the most potent toxin, and Witte the next highest. Inasmuch as consistent results were secured with but one of the American peptones, this was used for comparison with Witte's peptone and the special peptone studied.

The toxin produced with the special peptone has tested as high as 1000 M.L.D. per mil; it consistently tests 500 to 600 M.L.D. per mil. The Witte peptone has tested about 500 M.L.D. per mil, while the American brand has made toxin fluctuating between 100 and 300 M.L.D. per mil.

Experiments were made to determine whether the peptone employed in the toxin production had a detrimental effect when injected into animals; or whether the peptone was such that the growth of the diphtheria organism would produce by-products which were injurious when injected into animals.

Two series of guinea pigs were injected, one with broth before inoculating it with B. diphtheriæ for the production of toxin, another with toxin neutralized with an excess of antitoxin, using in each case lots prepared with Witte's peptone, the American brand, and the special peptone. Two guinea pigs were inoculated in each series with the material from the three peptones.

Table I shows the results of the injections of the peptone broth and Table II shows the results of the toxin-antitoxin experiment.

In Table I it will be noticed that the pigs injected with Witte's peptone showed no early ill effects but that during the period of the fifth to the seventh injections both suffered a drop in weight. With the American peptone one of the pigs lost weight steadily, finally became paralyzed and died; the mate first steadily lost in weight then gradually gained a little, and remained constant. The

*From the Biological Laboratories of Eli Lilly and Company, Indianapolis, Ind.

TABLE I*

DATE	INJECTION	WITTE'S PEPTONE		AMERICAN PEPTONE		EXPERIMENTAL PEPTONE	
		WT. PIG 268	WT. PIG 205	WT. PIG 206	WT. PIG 202	WT. PIG 263	WT. PIG 264
11-17	0.01 c.c.	250	280	250	215	295	280
11-19	0.02 "	235	265	235	195	285	260
20		245	275	240	210	315	280
21	0.04 "	245	270	225	200	300	275
22		245	275	225	195	295	280
23	0.08 "	240	260	220	190	285	270
24		230	260	215	200	280	260
26	0.16 "	210	250	205	180	275	275
27		225	255	205	180	260	265
28	0.32 "	215	245	195	165	260	260
30	0.64 "	210	235	175	170	250	260
12-1		200	235	185	170	255	260
3	1.28 "	240	255	185	180	300	275
4		235	260	175 paral.	180	290	275
6	1.5 "	260	280	Dead	200	310	305
7		255	285		205	310	300
8	1.5 "	250	260		200	290	285
10	1.5 "	245	265		180	290	265
11		265	290		215	290	275
12	1.5 "	270	285		220	310	310
13		265	280		220	335	300
14	1.5 "	270	285		200	330	305
15		275	290		210	320	300
16	1.5 "	260	285		200	325	310
17		265	280		205	320	305
18	1.5 "	260	275		215	315	315
19		265	275		210	315	320
20	1.5 "	260	270		210	310	315
21		255	270		210	305	315

*Injections consisted of samples from broth which had been sterilized and was ready to be inoculated with B. diphtheriæ for the production of toxin. The first five injections were made up to a volume of 0.5 c.c. by the addition of NaCl 0.85 per cent.

pigs on the special peptone showed a little loss of weight from the fifth to seventh injections and then rapidly increased in weight.

In Table II it will be seen that one of the pigs on Witte peptone steadily lost weight and finally died, whereas the mate kept fairly constant weight throughout the experiment. On the American peptone one pig constantly lost weight, finally became paralyzed and died. The mate, except for one drop in weight, remained about constant. Both the animals on the special peptone kept fairly constant weight.

In both experiments the danger period seemed to be from the fifth to eighth or ninth injection. The pigs on the special peptone did not lose as much weight and were more lively than the other pigs. Of those on Witte's peptone one died in the second experiment and one lost a great deal of weight in the first experiment. Of those on the American peptone one died in the first experiment while the other lost weight, and this was the case also in the second experiment; both the pigs which died developed a complete paralysis of the hind quarters which extended to the whole body.

While these tests are too few in number to be conclusive, they seem to

TABLE II*

DATE	INJECTION	WITTE'S PEPTONE		AMERICAN PEPTONE		EXPERIMENTAL PEPTONE	
		WT. PIG	WT. PIG	WT. PIG	WT. PIG	WT. PIG	WT. PIG
		265	262	210	203	267	270
11-17	0.01 c.c.	280	275	280	260	270	270
19		265	280	265	245	265	265
20	0.02	270	290	285	260	275	280
21		270	290	290	250	270	270
22	0.04	260	290	275	255	270	280
23		255	280	280	250	265	265
24	0.08	250	270	280	245	260	255
26	0.16	245	270	270	240	250	250
27		250	270	270	240	250	255
28	0.32	240	265	260	225	250	250
30	0.64	230	265	250	220	250	245
12-1		225	250	245	215	240	245
3	1.28	200	285	235	250	265	270
4		Dead	270	230 paral.	245	255	275
6	1.50		305	not 220 inj.	270	260	310
7			305	Dead	270	255	290
8	1.5		295		260	240	270
10	1.5		285		245	225	255
11			320		280	225	280
12	1.5		315		275	230	300
13			320		280	230	300
14	1.5		320		275	225	305
15			315		280	230	305
16	1.5		300		280	235	300
17			290		285	230	310
18	1.5		285		270	230	290
19			290		275	235	285
20	1.5		285		285	230	280
21			290		280	230	275

*Injections consisted of toxin neutralized by the addition of an excess of antitoxin. The material for all the injections was made up at the beginning of the experiment. The first five injections were made up to 0.5 c.c. by the addition of NaCl 0.85 per cent.

indicate that the toxicity of the special peptone is decidedly less than the American peptone and as low if not slightly lower than the Witte peptone.

The relationship of the L^+ dose to the M.L.D. of the toxins made from the three peptones was next determined. The ideal ratio of the M.L.D. to the L^+ dose is of course 1:100. By testing out the M.L.D. and the L^+ dose of toxins from the three peptones the following ratio of the M.L.D. to the L^+ dose was found:

Witte's peptone, 1:85
Special peptone, 1:110
American peptone, 1:150

One toxin from the American peptone gave a ratio as high as 1:180, the M.L.D. dose being 0.0025, the L^+ dose 0.4 c.c.

It should be noted that the Witte's peptone toxins were six months old or more before being tested while the special and American peptone toxins were fresh when tested. From these results it seemed that the special peptone produced a toxin which was more nearly ideal than the American brand.

OTHER BIOLOGICAL REACTIONS

The results given led to the belief that other biological tests were being confused by the use of different peptones. While the step into this field has been scarcely taken, it seems advisable at this time to report one or two instances that may lead to further investigation by others with the hope that if varying results are being obtained due to the use of different brands of peptone, some standardization may take place as regards peptones, to eliminate if possible at least one of the many errors to which most biological reactions are subject.

Several lots of typhoid vaccine were made up on mediums made from an American peptone (other than the American peptone employed in the production of diphtheria toxin). This vaccine was injected into rabbits and the rabbits then bled and their blood tested for agglutinin, using an antigen prepared from cultures grown on the same peptone. It was found that apparently no agglutinins were present.

However, using an antigen prepared from Witte peptone, agglutinins were found in the usual quantity while with antigens prepared on four other American peptones the results were negative except in the case of one American brand which showed agglutinins to be present in about half to three-fourths the amount shown by Witte's peptone. The results were obscured in the case of cultures on two of the American brands by the fact that they seemed to be spontaneously agglutinable. Using the special peptone, the same which was employed in the production of diphtheria toxin, the results showed that agglutinins were present in approximately the same quantity as those obtained with cultures on Witte's peptone.

The same was true with agglutination tests with meningococcus serum. The animals were injected with cultures grown on mediums made with American peptone. The serum showed a low agglutination titer when tested with cultures grown on American peptone media. With the same cultures carried on Witte's peptone and special peptone the serums showed a much higher agglutination titer.

CONCLUSIONS

Care should be exercised in the selection of peptone for the production of diphtheria toxin inasmuch as the peptone used may influence the physical condition of the animal injected with the toxin.

The peptone employed in the production of diphtheria toxin influences the potency of the toxin and what is of greater importance the ratio of the constituents of the toxin as shown by the ratio of the M.L.D. to the L^{+} dose.

The peptone used in the production of antigens employed in immunologic tests will influence the results of the tests.

LABORATORY METHODS

RECOMMENDATIONS OF THE COMMITTEE ON A STANDARD ROUTINE METHOD FOR THE ISOLATION AND IDENTIFICATION OF HEMOLYTIC STREPTOCOCCI FROM THROATS, SPUTA, AND PATHOLOGIC EXUDATES*

IN making these recommendations the committee is confronted by the necessity of sacrificing something in the direction of thoroughness and detail in order to recommend a method that will be simple and practical for use on a very large scale under the conditions obtaining in the army camps and cantonments.

The method recommended involves the isolation of the hemolytic streptococcus into bouillon from a blood agar plate and the use of the bouillon culture for various tests.

COLLECTION OF PATHOLOGIC MATERIAL

Throat swabs (tonsils and pharynx) are to be taken on ordinary sterile cotton swabs encased in sterile test tubes. These are to be sent promptly to the laboratory. Pus, if scant in amount, may also be collected on swabs. Considerable amounts of pus, pleural exudate, or sputum should be collected in sterile bottles or tubes (without antiseptic), taken promptly to the laboratory and there kept cold until cultured.

BLOOD AGAR PLATES†

Inoculation.—Swabs should be moistened with a drop or more of sterile salt solution unless they are obviously quite moist. Sputum should be washed as for the isolation of the pneumococcus and a kernel selected for culturing. A Gram stain of the sputum, swab, or exudate will often help to determine the amount of material that should be used for inoculation of the plate.

It is preferable to study both surface and deep colonies in the blood agar plate, hence material of known importance, such as pleural exudate, pus, and material from autopsies, should be suitably diluted, inoculated into fluid blood agar (at 45-50° C.) and poured into the petri dish. A small bit of the material may also be streaked out on the same or a different plate if desired.

For routine examination of swabs in large numbers surface inoculation only of blood agar plates is sufficient. It is recommended that only one swab be inoculated onto each plate. A convenient method of inoculation is to touch a spot near the edge of the plate with the moist swab and then with a platinum loop to smear the material from this spot back and forth across the surface of the medium with a view to securing greater dilution at points farthest from

*Report of a committee appointed by the Surgeon General.

†If streptococci are being sought for in material in which they may be quite rare, a preliminary growth in serum bouillon, dextrose blood bouillon, or cooked meat medium will serve to encourage the growth of streptococci above that of other organisms. If, on the other hand, it is desired to know the relative numbers of streptococci and other organisms present in the original material, it should be plated directly without preliminary "enrichment."

the spot touched by the swab. A cut into the agar by means of the edge of the loop for a short distance soon after it has left the inoculated spot will give some opportunity for growth in the depths of the agar.

Incubation.—Blood agar plates should be incubated at 37° C. in an inverted position for 18-24 hours before final observations are made. The atmosphere of the incubator should be kept humid by the exposure of a large surface of water in shallow pans on the floor of the incubator.

Study of Plates.—Isolated colonies with well defined colorless zones of hemolysis should be sought. There should be no pigmented (greenish or brownish) corpuscles visible under the low power of the microscope remaining next to or under the colony. The approximate number of such colonies (expressed as a percentage) with respect to all other colonies should be noted.

BOUILLON CULTURE

Inoculation.—A single typical isolated hemolytic colony is to be transferred to a tube of bouillon.

Incubation.—After incubation overnight or until there is a good amount of visible growth the bouillon culture is to be used as follows:

Study.—

1. A Gram stain is to be made and examined to make sure that the organism is a streptococcus and for a study of its morphology. The points to be noted are the length of the chains, the size, shape, and arrangement of the cocci in the chains, and any striking peculiarities.

2. A stock culture is to be made if it is desired to keep the strain in cultivation or if there is a possibility of the strain being used for further study later than the next day. If it is desired to save time in procuring the stock culture it may be inoculated from the blood agar plate at the same time the bouillon is inoculated provided the same colony is used, or it may be inoculated with a loop of the bouillon after the latter has been inoculated. The latter method serves to make a dilution of the material from the colony so that isolated colonies are obtained on the slant of the stock culture.

3. 0.5 c.c. of the bouillon culture is to be mixed with 0.5 c.c. of a 5 per cent suspension of washed rabbit blood corpuscles in physiologic salt solution and incubated in a water-bath at 37° C. for 2 hours. Streptococci which lake the blood completely in this time are to be regarded with suspicion. Markedly hemolytic pathogenic streptococci of human origin are known to produce laking of blood under these conditions.

4. To about 1 c.c. of bouillon culture add one-fifth volume of sterile ox bile. Observe for 1 hour at room or incubator temperature. Under certain conditions pneumococci on blood agar may cause hemolysis. Solubility in bile, however, serves to distinguish them from streptococci.

The above procedure is to be regarded as essential. The following additional tests are advised for more detailed study of cultures when time and conditions permit:

5. The bouillon culture to be replated (after proper dilution) into fluid blood agar so that the deep colony as well as the surface colony may be studied and as a check upon the purity of the culture.

6. The fermentation reactions towards lactose, mannite, salicin, inulin, raffinose and saccharose should be determined, the first three or four substances mentioned being of most importance.

7. A tube of milk should be inoculated and incubated for 7 days. During this time it should be noted whether coagulation occurs promptly, slowly, or not at all, and if it has not occurred the tube should be immersed in a boiling water bath for 10 minutes to see whether coagulation occurs under these conditions.

8. Inoculation of rabbits intravenously with not more than 1 c.c. of the fresh bouillon culture and inoculation of mice intraabdominally with much smaller amounts.

Notes and Details

BLOOD AGAR PLATES

Agar.—Standard beef infusion agar of the following composition shall be used:

	PER LITER OF MEDIUM
Aqueous extractives of	500 gms. of meat.
Agar-agar	20 gms.
Peptone	10 gms.
Salt	5 gms.

Final titratable acidity (after sterilization) to be between neutral and 0.5 per cent normal acid to phenolphthalein.

No dextrose or other fermentable substance should be added to the medium.

Kind of Blood.—Sterile defibrinated horse, human, or rabbit blood may be used. The sharpest results are probably obtained with horse blood but most hemolytic pathogenic streptococci are readily recognized on any of the kinds of blood mentioned.

Mixture of Blood and Agar.—The agar medium should be melted and cooled to 45 to 50° C. at which temperature 5 to 10 per cent of blood is added and thoroughly mixed into the agar.

Pouring of Plates.—A petri dish 9 cm. in diameter should receive 12 to 15 c.c. of blood agar, i. e., sufficient to make a layer 2 to 3 mm. thick.

Caution.—Sterile defibrinated blood may be kept in the refrigerator for several days but should not be used if it has begun to lake or if the sedimented corpuscles have become viscid so that it is difficult to shake them up into suspension.

Poured blood agar plates should not be kept on hand "ready for use" for longer than a few hours under ordinary conditions. If the surface of the medium becomes even slightly dry streptococci will not grow readily on it. If kept too long in the refrigerator the moisture collecting on the surface of the medium or undersurface of the lid is likely to cause confluence of colonies or to encourage the overgrowth of "surface spreaders."

BOUILLON CULTURE

The bouillon used should be standard meat infusion bouillon of similar composition to the agar described above. No dextrose should be added. No serum or ascitic fluid should be added if the bouillon culture is to be tested for solubility

in bile. The titratable acidity should be not above 0.5 per cent normal acid to phenolphthalein.

The bouillon culture should be used for the various tests only when it is quite fresh, not after it is two, three, or more days old, nor should tests be conducted by inoculation from one test medium to another. For later tests and experiments fresh bouillon cultures should be made directly from the stock culture.

STOCK CULTURES

Streptococci remain viable for many weeks or months on (1) blood agar slants, (2) standard agar slants to the surface of which a few drops of blood have been added, and (3) in bouillon to which a small percentage of blood has been added.

Blood agar slants are conveniently made by pouring fluid blood agar on the surface of previously prepared agar slants. There is obtained a layer of blood agar of uniform thickness on which the hemolytic action of the streptococcus colonies is readily observed for confirmation of the purity and character of the strain.

Dextrose should not be added to any of the stock culture media. Before being used any of the above media should be incubated for 48 hours after the blood has been added, to test their sterility. When slants are used the condensation fluid as well as the surface of the slant should be inoculated with the streptococcus. After inoculation any of these media should be incubated barely overnight and then kept cold.

SOLUBILITY IN BILE

Fresh undiluted ox bile may be autoclaved, filtered through paper, and again autoclaved. It is then ready for use as directed above.

SHIPMENT OF CULTURES

Cultures on the slant media described above may be shipped but for this purpose most of the condensation fluid should be pipetted off to prevent wetting of cotton plugs during shipment. It is also well to insert a cork stopper into the tube after the cotton plug has been burned off and pushed in.

The committee does not feel called upon to recommend in detail methods for the additional tests numbered 5, 6, 7 and 8 above, but is authorized to state that cultures of special interest may be sent to Rockefeller Institute for Medical Research, New York City, where they will be studied in detail. Each of these cultures should be accompanied by information regarding source, method, and date of isolation, the results of tests already conducted, and the medium on which it is grown.

Signed:

W. L. Holman,
Oswald T. Avery,
R. A. Kinsella,
J. Howard Brown.

June 1, 1918.

SIMPLIFIED GAS ANALYSIS

By J. J. R. Macleod, M.B., Cleveland, Ohio

THE extraordinary development of medical education in recent years, especially in this country, is attributed in large part to the introduction of practical laboratory courses in which simplified and fundamental experiments can be performed by the student himself. When the student is given the opportunity to "discover" some facts for himself, not only is his interest in other facts which he must accept on the authority of more highly trained investigators greatly enhanced, but he is in a better position to correlate them with what he already knows. This training is of value to him not alone in the particular science, such as physiology, to which the methods apply, but also in preparing him to estimate at their true value the signs and symptoms with which he will have to occupy his attention in the clinic. It also gives him a much greater enthusiasm for his work.

In many parts of physiology, particularly nerve-muscle physiology and the circulation, there is an adequate number of sufficiently simple experiments to make the practical courses of great value. But in other parts, this is far from being the case, and in none more conspicuously so than in respiration. To expect the student to comprehend the intricate problems connected with the exchange of gases between the blood and air and between the blood and tissues without himself doing some of the fundamental experiments, is as unreasonable as it would be to expect him to learn clinical medicine away from the patient. In order to make such experiments possible, considerable simplification of the apparatus and technic that have been used by the experienced investigator is essential, and it is proposed in this and subsequent articles to show how this has been accomplished in the classes under the writer's care.

There are two great difficulties in using gas-analysis apparatus with large classes of students. One is the sticking or "freezing" or breakage of stopcocks, and the other the large amount of mercury required for many of the processes. In the apparatus used in these experiments stopcocks are almost entirely replaced by screw clips, a device being introduced to equalize the gas pressure in the apparatus after the screw clip has been tightened, and very little mercury is employed. Much of the apparatus, especially that used for the analysis of alveolar air and the total respiratory exchange, can also be used with great advantage for routine clinical work without any significant sacrifice of accuracy.

NO. I. SIMPLIFIED PUMP FOR REMOVING AND ANALYZING THE BLOOD GASES

The first process to be described, namely, the removal of the gases from blood by a vacuum pump, is in many ways the most complicated of them all, and it is one which can have no important clinical application. Nevertheless, it is an experiment of very great value in the training of the student, since it demonstrates as no other method can that the blood carries a large amount of gas which is completely evolved only when the pressure is greatly reduced. The

apparatus is adapted from that of Leonard Hill,* the modifications being as follows:

1. The use of a syringe working in an oil-bath in place of the leveling tube with mercury.

2. The use of a substance to prevent foaming of the blood during the evacuation process, thus permitting a much smaller blood bulb to be used.

3. The collection of the gases in a graduated pipette instead of an eudiometer tube.

4. The preliminary evacuation of the blood bulb by means of one or other of the high-grade vacuum pumps which are usually part of the equipment of a physiological laboratory.

DETAILS OF METHOD

Place about 15 c.c. defibrinated ox blood in a 500 c.c. flask, and fill the latter with alveolar air by expiring deeply into it through a piece of wide-bore rubber tubing, or better, through glass tubes inserted through the stopper of a

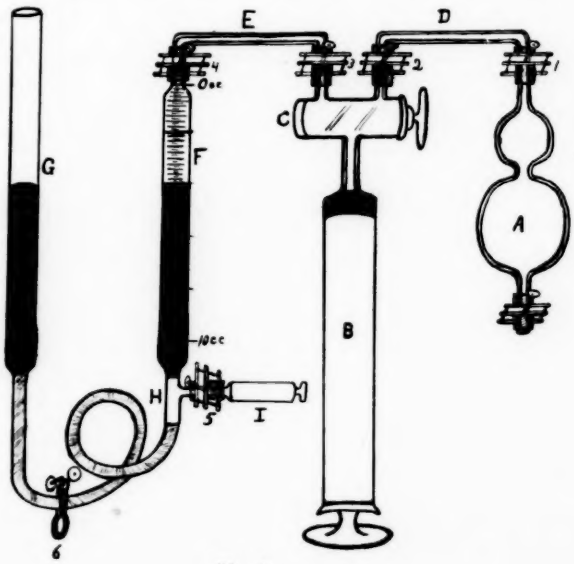

Fig. 1.

Fig. 2.

bottle filled with glass beads, which condenses and removes the water from the air. Rotate the flask so that the blood forms a thin film on the walls, but do not shake in such a manner as to cause the blood to froth. While rotating, occasionally expire through the tube into the flask so as to maintain the percentage of carbon dioxide constant. Continue this procedure for about three minutes and then close the flask. By this procedure the blood absorbs oxygen to full saturation, and carbon dioxide to the same extent as that of the blood in the pulmonary capillaries.

Meanwhile the bulb of the blood pump (Fig. 1, *A*) is evacuated by connecting it, by means of the attached piece of rubber tubing, to a vacuum pump (Geryk or Cenco-Nelson), which is operated until the manometer records as low a

*Hill, Leonard: Jour. Physiol., 1894, xvii, 353.

pressure as possible. The screw clip (1) is then tightened, leaving as long a piece of tubing beyond the clip as possible. A few drops of the antifoaming solution (caprylic alcohol or isoamylisovalerate) is then allowed to flow into the bulb. This is accomplished by taking about 0.5 c.c. of the fluid in a narrow-bored glass tube of sufficient external diameter to tightly fit the rubber tubing of the blood bulb (a 1 c.c. pipette with the delivery tapered end partially cut off). Before inserting the pipette into the rubber tubing, the lumen of the latter beyond the clip is filled with the antifoaming solution, so that no air may enter the bulb. The screw clip (1) is then very cautiously opened and about 0.1-0.2 c.c. of the solution allowed to run in, after which the clip is again screwed tight, the pipette removed, and the solution still in it replaced in the stock bottle.

Ten c.c. of blood is now placed in the bulb. To accomplish this remove blood from the flask by means of the special 10 c.c. pipette (see Fig. 2), using only gentle suction and filling to the upper mark. Squeeze all air out of the tub-

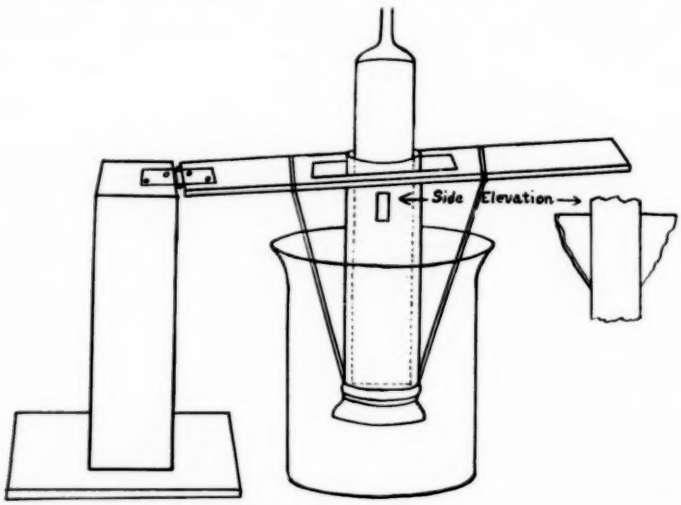

Fig. 3.

ing on the blood bulb, and then insert the end of the pipette in the tubing, being careful to see that no air bubbles are present at the union. Holding the pipette and blood bulb vertically, cautiously unscrew the clip (1) and allow the blood to flow from the pipette into the bulb until the lower mark on the former is reached. The capacity between the two marks is 10 c.c. After tightening the screw clip, remove the pipette and squeeze out the blood left in the tubing.

The blood pump must now be prepared. This consists of a 50 c.c. all-glass (Luer) syringe (*B*), with vaseline between the walls and piston, the nozzle being connected by thick-walled rubber tubing with the single tube of a three-way stopcock (*C*). Of the other tubes of the stopcock, one (*D*) runs to connect, by narrow-bore glass tubing, with the blood bulb and the other (*E*) to the gas burette (*F*). (A 10 c.c. graduated pipette is satisfactory.) To avoid all risk of air leakage into the syringe, this is manipulated in an oil-bath,* as shown in Fig. 3. A brass tube of a diameter slightly greater than that of the syringe is

*Any high-grade mineral oil such as Polarine or Mobilol can be used.

allowed to rest on the shoulder at the end of the piston. To opposite sides of this tube, near its upper end, are soldered two projections (see side elevation), on which rest the wooden lever, which is hinged to a block as shown in the illustration. Two wires also connect the handle of the piston with the lever. The syringe must be firmly held in a clamp at its upper end, and cotton or asbestos is placed between the clamp and the glass, so as to prevent breakage and permit of some lateral motion when the lever is manipulated.

The first step in preparing the blood pump is to get rid of all the dead space in the tubing and connections. This is readily accomplished, for *E* by turning stopcock *C* so that *E* communicates with *B*, raising the leveling burette (*G*), and simultaneously withdrawing the piston of the syringe, by depressing the lever, until about 20 mm. of mercury has collected on the top of the piston. The stopcock is then turned so that *B* and *D* are connected and the piston raised until all the air is expelled and mercury completely fills tube *D*. Any drops of mercury falling from the open end of *B* must be caught in a small beaker. The mercury left on the top of the piston seals this completely during the subsequent manipulations.

After squeezing all air out of the tubing on the blood bulb, this is now connected with *D* and immersed in a jug containing water at 45° C. Having turned *C* so that *B* communicates with *D*, the piston is then depressed to about the 20 c.c. mark, and while still depressed the screw clip (1) is opened. About this time the blood will begin to boil and the gases given off from it will pass into the vacuum above the mercury in the syringe. *C* is turned so that *B* is closed off and the piston allowed slowly to ascend. (It must not be allowed to ascend too rapidly, since this might break the syringe.) The gas which has collected in the syringe is now expelled into the burette (*F*) by turning *C* so that *B* and *E* communicate and pressing up the piston. After all the gas is out of the syringe, mercury is allowed to run into *E* a short distance, being careful not to allow any to get into *F*. This first process obviously removes only a small fraction of the total gas in the blood, and it must be repeated several times exactly as described above, until no more gas can be secured. The dislodgment of the gas from the blood is greatly accelerated by warmth and by occasionally removing the bulb from the water-bath and shaking briskly.

It is now necessary to measure and analyze the evolved gas. For this purpose the piston is cautiously pushed up, with *E* and *B* in communication, until mercury stands at the zero mark on the neck of the gas burette. The clip (4) is then screwed down and the leveling burette (*G*) lowered until the menisci stand at the same level in it and the burette. This brings the gas to atmospheric pressure and the volume is read and noted. The reading gives the c.c. of gas in 10 c.c. blood. The volume should be reduced to standard temperature and pressure (for calculation see p. 431 of this JOURNAL). To analyze the gas a 40 per cent solution of sodium hydroxide is sucked from a watch glass into the 2 c.c. all-glass syringe (*I*), and the tube attached to the nozzle inserted in the side tube (*H*). All air must be expelled from this tube. With the pinchcock (6) closed, the clip (5) is opened, while gentle pressure is being maintained on the piston of the small syringe so that the mercury may not run into it. The NaOH runs up to the top of the mercury column (*F*), and when it is all in,

clip 5 is again screwed down. The syringe (*I*) is removed and *F* inverted several times so that the carbon dioxide in the gas contained in it may be thoroughly absorbed. On now opening clip 6, the mercury will rise in *F*, and by adjusting the leveling tube the shrinkage in volume due to the absorption of CO_2 can be ascertained and the percentage of this gas determined. The reading is taken which corresponds to the top of the NaOH solution, a similar amount of NaOH solution being placed on the top of the mercury in the leveling tube. Care must be taken to see that all the CO_2 is absorbed.

To absorb the oxygen, about a gram of pyrogallic acid is dissolved in 2 c.c. of water in the watch glass, the solution is introduced into *F*, and the further manipulations conducted in the same manner as for the NaOH solution. The gas which remains when both CO_2 and O_2 are absorbed is nitrogen. There should not be more than 0.1-0.2 c.c., any larger amount being due to air leakage into the apparatus during the manipulations. If any considerable amount of nitrogen is left, its volume should be measured, and by subtracting 0.2 from this, the volume of O_2 that must have been introduced, as air, with it can be ascertained and subtracted from the actually observed O_2. By taking proper precautions, however, the residual nitrogen should never be more than 0.3-0.5 c.c.

When the analysis is completed, the mercury is run out from the burette by the side tube (*H*), after removing the stopcock (*C*), and the burette thoroughly washed with water. The mercury and alkali pyrogallate solution (which is now brown in color) are then washed in running water until the washings react neutral to litmus paper. The mercury should then be transferred to a separating funnel containing a dilute solution of sulphuric acid. The blood bulb should also be cleaned immediately, since otherwise a sticky precipitate which is difficult to remove adheres to the walls.

SIMPLE METHOD OF MEASURING ANTISHEEP AMBOCEPTOR CONTENT OF HUMAN SERUM AND CORRECTING FOR IT IN WASSERMANN TESTS

By J. J. Seelman, M.D., Milwaukee, Wis.

NATIVE antisheep amboceptors are present in varying amounts in most human bloods. It has long been evident to serologists that this factor introduces a source of error in complement-fixation tests in which the sheep hemolytic system is employed. If the hemolytic system is to perform its function of indicator with precision its action must be uniform for every serum tested in a given test. In the classical Wassermann test the native antisheep amboceptors are ignored. As a result the carefully titrated system of known hemolytic strength becomes a system of unknown strength the moment it is added to the antigen-serum-complement mixture. If it is conceded that a carefully titrated hemolytic system is essential to accurate work, it necessarily follows that any factors which tend to throw this system out of adjustment the moment it is about to exercise its function of indicator should, if possible, be removed.

If a human hemolytic system is employed, as in the Noguchi test, the anti-

sheep amboceptors can, of course, be ignored. Practical considerations have, however, prevented the general adoption of the human hemolytic system. It is much more difficult to immunize rabbits against human corpuscles than against sheep corpuscles. The hemolytic titer for the former can never be brought as high as for the latter, while the agglutinating titer is usually much higher. Isohemolysins as well as isoagglutinins also interfere with the accuracy of this system.

Antisheep amboceptors can be removed by subjecting the serum to the action of sheep corpuscles and subsequently removing the latter by centrifugation. This requires additional handling and repipetting of sera, consumes considerable time and increases the chances of error. There is also unquestionably an osmotic interchange between corpuscles and serum, and just how far this may influence the specific behavior of the serum in the test has not been determined. That serum is considerably more anticomplementary after this treatment than before has been demonstrated.

The titration of each serum to determine its antisheep amboceptor content can, of course, be carried out, but requires an amount of labor inconsistent with the requirements of routine work.

I have for some time used, with complete satisfaction, a simple method which is practically accurate, and requires the setting up of but one tube for each serum to be tested in addition to an amboceptor titration.

Essentially the method consists of utilizing the tubes of an amboceptor titration as standards by which to measure the hemolyzing power of the serum to be examined. The detailed technic must vary somewhat with the methods employed in different laboratories.

In our laboratory we use one-fourth Wassermann quantities. Our amboceptor is dried on filter paper in which condition it keeps its titer unchanged for at least six months. As any one batch of amboceptor is consumed in much less time than this, the originally ascertained titer can always be accepted as correct. The titer of a new amboceptor is established by comparisons with the old, and by titrations with pooled guinea pig serum. The amboceptor is diluted so that the dose (two units) is .14 c.c. and with it as a standard we titrate the complement before each test. Along with this complement titration, the native amboceptor content of each serum to be examined is ascertained as follows:

Two series of tubes are set up. One series is an amboceptor titration, consisting of seven tubes, each receiving .25 c.c. of a 1:10 guinea pig serum dilution, .25 c.c. 5 per cent corpuscle suspension, and increasing amounts of amboceptor dilution, .02, .04, .06, .08, .1, .12 and .14 c.c. respectively. The second series consists of one tube for each serum to be tested, receiving each .25 c.c. complement dilution, .25 c.c. corpuscle suspension and .05 c.c. of its respective, inactivated serum, but no amboceptor. This set-up is placed in the water-bath at 37.5 C. for one-half hour. With an average complement the .14 c.c. amboceptor tube will begin to hemolyze in about five to six minutes and will be completely hemolyzed in about ten to twelve minutes, varying somewhat with different guinea pig sera. When about 75 per cent hemolysis has taken place in the .14 c.c. amboceptor tube it is taken out and compared with each of the serum tubes and the sera of those tubes which correspond to it in degree of hemolysis

are considered as having a value of .14 c.c. amboceptor. The same procedure is carried out with the .12, .1 and .08 c.c. amboceptor tubes when each has attained about 75 per cent hemolysis. At the end of the half-hour the .08 c.c. amboceptor tube is usually completely hemolyzed and the .06 c.c. shows slight inhibition. At this time, without waiting for further hemolysis, the .06, .04 and .02 c.c. amboceptor tubes are compared with the remaining serum tubes and each of these latter is given an amboceptor value corresponding to the amount of amboceptor contained in the amboceptor tube with which it compares. The comparisons, of course, are not always exact, and when they fall between two amboceptor tubes the selection is made between them. For instance, if a serum tube falls between the .06 and .08 c.c. amboceptor tube, it is read as containing .07 c.c. amboceptor.

In the test proper the required allowances are made. If a serum was shown to contain a native amboceptor value corresponding to .14 c.c. (the full dose) of the amboceptor dilution to be used, it receives no amboceptor whatever in the test; if its value is less than this, it receives the difference between its value and .14; if its value is less than .02 c.c. it receives the full dose of amboceptor.

Not infrequently sera are encountered which hemolyze faster than the .14 c.c. amboceptor tube. If the difference is only slight, it is ignored. If it is considered sufficient to act as a source of error, the native amboceptor is removed altogether and the serum given the full dose in the test.

For the purposes of the above described native amboceptor determinations, the complement titer of the guinea pig serum is immaterial, the only condition being that the same amount of guinea pig serum and the same amount of corpuscles are used in the amboceptor standards as are used in the serum unknowns. For this reason, when complement titrations are made before the Wassermann test, the native amboceptor determinations can be made along with the complement titration, and require no additional time except that consumed in setting up the necessary tubes. If no complement but only an amboceptor titration is made, the native amboceptor determinations can be made by the simple addition of the serum tubes, as above described, to the usual amboceptor titration.

Following are the native amboceptor determinations made on 500 sera recently tested in our laboratory with an amboceptor dilution of which the dose (two units) was .14 c.c.:

AMBOCEPTOR VALUE	
Less than .02 c.c.	166
.02 " to .04 c.c.	79
.04 " " .06 "	75
.06 " " .08 "	56
.08 " " .10 "	30
.10 " " .12 "	29
.12 " " .14 "	25
.14 " " .14 " +	19
.14 " " .14 " ++	12
.14 " " .14 " +++	9

That the correction of these wide variations of native antisheep amboceptor content must add considerably to the accuracy of the Wassermann test is self-evident.

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EDITORIALS

Substitutes for Blood in Transfusion

THERE exists, as Rous and Wilson[1] say, a great and urgent need for an injection fluid that can be satisfactorily employed instead of blood for transfusion in cases of hemorrhage. That this need is greatest at or near the battle fronts in Europe goes without saying. Nevertheless there is a constant need of such a fluid in everyday emergency work at home.

The reason that blood is the ideal transfusion fluid is not that it is blood nor that it contains hemoglobin or other blood substances, but because the liquid (the water) that it contains is held by the colloids of the fluid in such a way that it is held by them for a longer period than so much pure water would be and therefore it remains longer in the vessels and gives the heart something to push against, so to speak. If one introduces pure water into the vessels of the body it is almost immediately given up and excreted by the kidneys. Water held by colloids, on the contrary, tends to be held in the body until the colloids holding the water are split up by the ferments of the body and the water is set free. Salt solutions not held in colloidal combination act as does pure water. Obviously the ideal fluid for injection after hemorrhage is blood plasma, for it is a colloidal solution in which the water is held in a physiologic stable way. But, also ob-

viously plasma is not always obtainable on short notice. It has been shown that when more than half the total calculated blood volume had been taken from an animal and when the carotid pressure had fallen to the physiologic zero, the pressure was instantly and permanently restored to normal by injecting an equivalent amount of plasma. A saline solution on the other hand brought about only a slight transient recovery of the pressure.

As substitutes for plasma or blood in transfusion Hogan[2] has recommended and used a 2.5 gelatin solution, and Bayliss[3] a 6 per cent gelatin or a 7 per cent gum acacia solution. The acacia has the advantage over gelatin that it can be sterilized without danger of hydrolyzing it and thereby rendering it useless. Boiling it does no damage. Also acacia is protein-free and therefore will not produce anaphylaxis. A 2 per cent acacia solution at first raises the lowered blood pressure to normal but the rise is very transient. A 4 per cent solution is more satisfactory, but this, or even a 5 per cent solution, is not effective in all cases. Six or 7 per cent is required if one is to bring back the normal pressure in an organism depleted of its fluid reserves.

As Rous and Wilson say, the needs for a blood substitute may be widely different in different cases. When the hemorrhage has been rapid and has been completely checked, almost any harmless isotonic solution will tide the patient over. It matters little that the fluid will soon leave the vessels, for the patient's fluid reserves are almost intact, as is his ability to manufacture a plasma rapidly. At the other extreme are those instances in which the blood has been draining steadily away and there remains in the body no source of an immediate restoration of fluid. Here half-measures can not suffice. A fluid must be furnished which will take the place, over many hours, of the lost blood bulk. Except for the blood or plasma of other human beings, fluids containing from 6 to 7 per cent of gum acacia are the best at present available for the purpose. Intermediate cases can undoubtedly be much helped by a 2 or 3 per cent acacia solution or by Hogan's solution. In view of our ignorance of the after-effects of these foreign substances it is advisable not to inject more than the needs of the case demand.

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—*P. G. W.*

The Duty of the Employer in the Reconstruction of the Crippled Soldier

WE must count on the return from the front of thousands of crippled soldiers. We must plan to give them on their return the best possible chance for the future.

Dependence cannot be placed on monetary compensation in the form of a pension, for in the past the pension system has proved a distinct failure in so far as constructive ends are involved. The pension has never been enough

to support in decency the average disabled soldier, but it has been just large enough to act as an incentive to idleness and semi-dependence on relatives or friends.

The only compensation of real value for physical disability is rehabilitation for self-support. Make a man again capable of earning his own living and the chief burden of his handicap drops away. Occupation is, further, the only means for making him happy and contented.

Soon after the outbreak of hostilities the European countries began the establishment of vocational training schools for the rehabilitation of disabled soldiers. They had both the humanitarian aim of restoring crippled men to the greatest possible degree and the economic aim of sparing the community the burden of unproductivity on the part of thousands of its best citizens. The movement had its inception with Mayor Edouard Herriot of the city of Lyons, France, who found it difficult to reconcile the desperate need for labor in the factories and munition works while men who had lost an arm or a leg but were otherwise strong and well were idling their time in the public squares. He therefore induced the municipal council to open an industrial school for war cripples which has proved the example and inspiration for hundreds of similar schools since founded throughout France, Italy, Germany, Great Britain and Canada.

The disability of some crippled soldiers is no bar to returning to their former trade, but the injuries of many disqualify them from pursuing again their past occupation. The schools of training prepare these men for some work in which their physical handicap will not materially interfere with their production.

The education of the adult is made up largely of his working experience. The groundwork of training in his past occupation must under no circumstances be abandoned. The new trade must be related to the former one or be, perhaps, an extension or specialization of it. For example, a man who had done manual work in the building trades may by instruction in architectural drafting and the interpretation of plans be fitted for a foreman's job, in which the lack of an arm would not prove of serious handicap. A trainman who had lost a leg might wisely be prepared as a telegrapher, so that he could go back to railroad work, with the practice of which he is already familiar.

Whatever training is given must be thorough, for an adult can not be sent out to employment on the same basis as a boy apprentice. He must be adequately prepared for the work he is to undertake.

The one-armed soldier is equipped with working appliances which have supplanted the old familiar artificial limb. The new appliances are designed with a practical aim only in view; they vary according to the trade in which the individual is to engage. For example, the appliance for a machinist would be quite different from that with which a wood turner would be provided. Some appliances have attached to the stump a chuck in which various tools or hooks can interchangeably be held. The wearer uses these devices only while at work; for evenings and holidays he is provided with a "dress arm" which is made in imitation of the lost natural member.

An important factor in the success of re-educational work is an early start, so that the disabled man shall have no chance to go out unemployed into the community. In even a short period of exposure to the sentimental sympathy of family and friends, his "will to work" is so broken down that it becomes difficult again to restore him to a stand of independence and ambition. For this reason, therefore, the plan for his future is made at as early a date as his physical condition admits, and training is actually under way before the patient is out of the hospital.

In the readjustment of the crippled soldier to civilian life, his placement in employment is a matter of the greatest moment. In this field the employer has a very definite responsibility.

But the employer's duty is not entirely obvious. It is, on the contrary, almost diametrically opposite to what one might superficially infer it to be. The duty is not to "take care of" from patriotic motives, a given number of disabled men, finding for them any odd jobs which are available, and putting the ex-soldiers in them without much regard to whether they can earn the wages paid or not.

Yet this method is all too common. A local committee of employers will deliberate about as follows: "Here are a dozen crippled soldiers for whom we must find jobs. Jones, you have a large factory; you should be able to take care of six of them. Brown, can you not find places for four of them in your warehouse? And Smith, you ought to place at least a couple in your store."

Such a procedure can not have other than pernicious results. In the first years of war the spirit of patriotism runs high, but experience has shown that men placed on this basis alone find themselves out of a job after the war has been over several years, or in fact, after it has been in progress for a considerable period of time.

A second weakness in this method is that a man who is patronized by giving him a charity job, comes to expect as a right such semi-gratuitous support. Such a situation breaks down rather than builds up character, and makes the man progressively a weaker rather than a stronger member of the community. We must not do our returned men such injury.

The third difficulty is that such a system does not take into account the man's future. Casual placement means employment either in a makeshift job as watchman or elevator operator such as we should certainly not offer our disabled men except as a last resort—or in a job beyond the man, one in which, on the cold-blooded considerations of product and wages, he can not hold his own. Jobs of the first type have for the worker a future of monotony and discouragement. Jobs of the second type are frequently disastrous, for in them a man, instead of becoming steadily more competent and building up confidence in himself, stands still as regards improvement and loses confidence every day. When he is dropped or goes to some other employment, the job will have had for him no permanent benefit.

Twelve men sent to twelve jobs may all be seriously misplaced, while the same twelve placed with thought and wisdom and differently assigned to the same twelve jobs may be ideally located. If normal workers require expert

and careful placement, crippled candidates for employment require it even more.

The positive aspect of the employer's duty is to find for the disabled man a constructive job which he can hold on the basis of competency alone. In such a job he can be self-respecting, be happy, and look forward to a future. This is the definite patriotic duty. It is not so easy of execution as telling a superintendent to take care of four men, but there is infinitely more satisfaction to the employer in the results, and infinitely greater advantage to the employee. And it is entirely practical, even in dealing with seriously disabled men.

A cripple is only debarred by his disability from performing certain operations. In the operations which he can perform, the disabled man will be

BACK TO THE OLD JOB.

Most of our wounded will be able to resume their former occupations. Although he lost both legs, this soldier will continue in his profession as a draftsman. At present he is being physically reconstructed at Walter Reed Hospital, Washington, D. C., but as soon as his artificial limbs are fitted he will leave. Meanwhile, the most effective curative agent is his occupation with mechanical drafting. (Courtesy "Carry On.")

just as efficient as his non-handicapped colleague, or more so. In the multiplicity of modern industrial processes it is entirely possible to find jobs not requiring the operations from which any given type of cripples are debarred. For such jobs as they can fill the cripple should be given preference.

Thousands of cripples are now holding important jobs in the industrial world. But they are men of exceptional character and initiative and have, in general, made their way in spite of employers rather than because of them. Too many employers are ready to give the cripple alms, but not willing to ex-

pend the thought necessary to place him in a suitable job. This attitude has helped to make many cripples dependent. With our new responsibilities to the men disabled in fighting for us, the point of view must certainly be changed. What some cripples have done, other cripples can do—if only given an even chance.

The industrial cripple should be considered as well as the military cripple, for in these days of national demand for the greatest possible output there should not be left idle any men who can be made into productive workers.

With thoughtful placement effort, many men can be employed directly on the basis of their past experience. With the disabled soldiers who profit by the training facilities the government will provide, the task should be even easier.

This, then, constitutes the charge of patriotic duty upon the employer:

To study the jobs under his jurisdiction to determine what ones might be satisfactorily held by cripples. To give the cripples preference for these jobs. To consider thoughtfully the applications of disabled men for employment, bearing in mind the importance of utilizing to as great an extent as possible labor which would otherwise be unproductive. To do the returned soldier the honor of offering him real employment, rather than proffering him the ignominy of a charity job.

If the employer will do this, it will be a great factor in making the complete elimination of the dependent cripple a real and inspiring possibility.

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